Zinc Chloride Health Advisory

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Zinc Chloride

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PREFACE

This report was prepared in accordance with the Memorandum of Understanding between the Department of the Army, Deputy for Environmental Safety and Occupational Health (OASA(IL&E)), and the U.S. Environmental Protection Agency (EPA), Office of Water (OW), Office of Science and Technology, for the purpose of developing drinking water Health Advisories (HAs) for selected environmental contaminants, as requested by the Army.

Health Advisories provide specific advice on the levels of contaminants in drinking water at which adverse health effects would not be anticipated and which include a margin of safety to protect the most sensitive members of the population. A Health Advisory provides health effects guidelines and analytical methods and recommends treatment techniques on a case-by-case basis. These advisories are normally prepared for one-day, ten-day, longer-term, and lifetime exposure periods where available toxicological data permit. These advisories do not condone the presence of contaminants in drinking water, nor are they legally enforceable standards. They are not issued as official regulations and they may or may not lead to the issuance of national standards or Maximum Contaminant Levels (MCLs).

This report is the product of the Health Advisory Development process. Available toxicological data (as provided by the Army and as found in open literature sources) on the munitions chemical zinc chloride have been reviewed, and relevant findings are presented in this report in a manner that allows for evaluation of the data without continual reference to the primary documents. Additional data on the properties of other soluble zinc compounds are also presented. This report has been submitted for critical internal and external review by the EPA.

I would like to thank the authors who provided the extensive technical knowledge required for the preparation of this report. I am grateful to the members of the EPA Toxicology Review Panel who took time to review this report and to provide their invaluable input, and I would like to thank Dr. Edward Ohanian, Chief, Human Risk Assessment Branch, and Ms. Margaret Stasikowski, Director, Health and Ecological Criteria Division, for providing me with the opportunity and encouragement to be a part of this project.

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Officer of Water

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EXECUTIVE SUMMARY

Zinc is a naturally occurring element commonly found in the earth's crust. Zinc is a bluish-white metal in its pure form, but also can exist as a number of divalent inorganic compounds such as zinc chloride, zinc sulfate, and zinc oxide. Although zinc occurs naturally in the environment, zinc may be released to the environment from a number of industrial processes including galvanization, wood preservation, soldering, dry-battery cell production and organic synthesis. In addition, zinc chloride may be introduced into the environment through its use as a military screening smoke. In the environment, zinc hydrolyzes when dissolved in water. Adsorption of zinc to sediments and soils and the bioaccumulation of zinc have been reported to occur.

The pharmacokinetics of zinc have been well studied in animals and humans. Zinc is absorbed moderately well following oral intake. Absorption through the skin is minimal while data on absorption following inhalation of particulate zinc is limited. Radiolabeled zinc (administered as zinc chloride) mainly distributes to the intestines, prostate, liver and kidney with kidney levels remaining highest after intravenous administration. Metallothionein plays an important role in regulating zinc homeostasis. Excretion is mainly through the feces.

Following acute oral exposures of humans to high doses, up to 1,000 mg/kg, of zinc, symptoms including vomiting, diarrhea, lethargy, and irritation of the mouth, throat and stomach may occur. Acute symptoms of zinc toxicity from exposure via inhalation include dyspnea, chest constriction, retrosternal and epigastric pain, hoarseness, stridor, cough, lacrimation, expectoration and an occasional hemoptysis. Pale grey cyanosis usually develops, pulse is elevated, fever is present and bronchopneumonia can develop. Edema is widespread. Death is usually due to respiratory insufficiency. Effects are related to the hygroscopic nature of the inhaled zinc particles which combine with moisture in the lungs to form caustic substances.

Oral exposures to zinc (as the gluconate) for longer periods of time (6-12 weeks) were shown to reduce serum erythrocyte superoxide dismutase [E-SOD] and ceruloplasmin (biomarkers of copper stakes) as well as HDL levels.

In animal studies, oral LD_{50}s as well as average lethal oral doses have been reported for zinc compounds in several species. Zinc chloride causes both skin and eye irritation, and percutaneous toxicity has been demonstrated. Oral exposure to approximately 100 mg/kg/day of zinc chloride for up to six weeks has been shown to precipitate a deficiency syndrome when combined with a synthetic diet low in pantothenic acid. Renal damage was observed in rats exposed orally to 190.6 mg/kg/day zinc acetate for 90 days. Several studies indicate that high doses of various forms of zinc can interfere with reproductive function at doses as low as 25 mg/kg/day and is fetotoxic.

Mutagenicity and carcinogenicity studies have largely yielded equivocal or negative results. Zinc chloride was not mutagenic in a variety of bacterial (Salmonella typhimumum, Escherichia coli, Saccharomyces cerevesiae) and in vitro mammalian (Chinese hamster ovary and embryo cells, human lymphocytes and white blood cells) cell systems. Zinc chloride also did not cause chromosomal

aberrations in mouse bone marrow cells when administered to the animals in an in vivo assay.

Health advisory values for zinc chloride are based upon measuring zinc (Zn^{++}) in water. Based on the available animal toxicity data, the HA for One-day and Ten-days is 5 mg/L for the 10 kg child. The Longer-term HA for the 10 kg child is 3 mg/L and for the 70 kg adult is 10 mg/L. The Lifetime HA is 2 mg/L. These values are considered protective against toxic effects for the most sensitive members of the population. The essentiality of zinc was considered in the derivation of these HA values. Currently, adequate available data to assess the carcinogenic risk of zinc are inadequate. Using the EPA criteria for classification of carcinogenic risk, zinc chloride and other zinc compounds currently meet the criteria for category D, not classifiable as to human carcinogenicity. This category is for agents with inadequate human and animal evidence of carcinogenicity or for which no data are available.

ZINC CHLORIDE AND OTHER ZINC COMPOUNDS

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Water (OW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The Advisories are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10 percent of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. For those substances that are known or probable human carcinogens, according to the Agency's classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linearized multistage model with 95% upper confidence limits on risk. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit and Probit models. Current understanding of the biological mechanisms involved in cancer do not suggest that any one of these models is able to predict risk more accurately than another. Because each model is based upon differing assumptions, the estimates that are derived can differ by several orders of magnitude.

The major emphasis of this Health Advisory is on zinc chloride. However, because in water zinc chloride and other zinc compounds hydrolyze to form ionic zinc (Zn^{++}), a review of zinc chloride health effects must include observations and data associated with all forms of ionizable zinc compounds. Throughout this document when the term "zinc" is used without identifying it as a salt (e.g., chloride, acetate, sulfate, etc.) or other compound (e.g., zinc oxide), it refers to the ion.

II. GENERAL INFORMATION AND PROPERTIES

Cas No.

Zn:	7440-66-6
$ZnCl_2$:	7646-85-7
$ZnSO_4 \cdot 7H_2O$:	7446-20-0
ZnO:	1314-13-2

Synonyms

Zn: Zinc
$ZnCl_2$: Zinc chloride, butter of zinc;
$ZnSO_4 \cdot 7H_2O$: Zinc sulfate heptahydrate, Op-Thal-Zin, Verazinc;
ZnO: Zinc oxide, flowers of zinc, philosopher's wool, zincite.

Uses

Worldwide yearly production of zinc averages several million metric tons. Annual industrial demand in the United States is 1.5 metric tons. Zinc metal is used extensively in the United States in the machine, building and automotive industries as a component of galvanized steel (NRC, 1979). Zinc oxide, the most important inorganic zinc compound, is used in the rubber vulcanizing process, pigments, paints, ceramics and pharmaceuticals. Zinc sulfate is used in plastics production; zinc chloride is used in batteries; zinc sulfide and zinc silicate are used as phosphors in cathode ray tubes; and zinc chromate is used as a wood preservative. Zinc chloride, zinc gluconate, zinc oxide, zinc stearate, and zinc sulfate are used as additive nutrients in foods and dietary supplements; zinc carbonate is used as a dietary supplement for farm animals. Zinc borate is used as a fire retardant. Zinc sulfate and zinc chloride are added to potable water to reduce corrosion.

Zinc chloride is a highly deliquescent, white, granular or crystalline substance that is used commercially in textiles, adhesives, wood preservation, embalming fluids, deodorants and numerous other commercial processes. It has been used medicinally as a dentifrice, astringent and antiseptic and is used by the military as a screening smoke. Zinc chloride is highly soluble in water and several organic solvents. It fluoresces in solution, and the hydrated form evaporates to produce a white, semi-solid mass similar in consistency to butter, hence its synonym, butter of zinc. Its chemical and physical properties are listed in Table II-1.

Zinc chloride is produced by the action of hydrochloric acid on zinc, zinc oxide or zinc sulfide ore (Cumpston, 1983) and may be purified by recrystallization. The commercial product is 95% pure with the remainder being water and some oxychloride ($ZnCl_2 \cdot ZnO$) (Hill et al., 1978). It is trimorphic in nature with α-, ß- and γ-forms. The commercial product is either α-, γ-, or α- plus γ-zinc chloride (Farnsworth and Kline, 1973 as cited in Hill et al., 1978).

In its solid form, zinc chloride is odorless but corrosive; as an aqueous solution it is highly acidic and may cause chemical burns. Its fumes act as an irritant to the eyes and mucous membranes. Zinc chloride smoke, (the military screening agent), is produced when mixtures of zinc oxide, hexachloroethane (HCE) and 10% calcium silicide or, more recently, 9% grained

aluminum is ignited. The resulting chemical reaction produces mostly particulate zinc chloride along with free carbon, calcium carbonate and silica (Macaulay and Mant, 1963). The highly hygroscopic zinc chloride combines with the moisture in the air to produce hydrochloric acid and zinc oxychloride. In an enclosed space, the particulate zinc chloride can be inhaled and hydrolyzed in the lungs, resulting in widespread mucosal damage.

Table II-1

Chemical and Physical Properties of Zinc Compounds[a]

Properties	Zinc	Zinc chloride	Zinc sulfate heptahydrate	Zinc oxide
Chemical Formula	Zn	$ZnCl_2$	$ZnSO_4 \cdot 7H_2O$	ZnO
Atomic/Molecular Weight	65.38	136.29	287.54	81.4
Physical State (25°C)	Solid; bluish-white, lustrous metal	Solid, white hexagonal crystals or powder, deliquescent	Solid, rhombic crystals efflorescent	Solid, white hexagonal crystals
Boiling Point	908°C	732°C	280°C[b]	None found
Melting Point	419.5°C	290°C	100°C	1,975°C
Density	7.14 (25°C)	2.91	1.96	5.67
Vapor Pressure	1 mm Hg (487°C)	None found	1 mm Hg (428°C)	None found
Water Solubility	Insoluble	432 g/100 mL (25°C)	96.5 g/100 mL (20°C)	Insoluble
Specific gravity (25°C)	7.14	2.91	1.96	5.67
Log Octanol/Water Partition Coefficient	Not applicable	None found	None found	None found
Taste Threshold (Water)	None found	None found	None found	None found
Odor Threshold (Water)	None found	None found	None found	None found

[a] References: Budavari, 1989; Weast, 1987; Sax, 1975)
[b] Temperature at which the water of hydration is lost. No boiling point was available for $ZnSo_4$.

III. OCCURRENCE

A. Zinc Chloride

Zinc is ubiquitous in nature, found in most foodstuffs, water and air, and an essential trace nutrient. Zinc in the soil is taken up by plants. The average daily consumption is estimated at 12-15 mg, mostly from food (Klaassen et al., 1986). Zinc chloride, an inorganic salt of zinc, is produced by the action of hydrochloric acid (HCl) on zinc or zinc oxide. Its introduction into the environment may result from industrial effluent from such processes as galvanizing, wood preservation, soldering, dry-battery cell production, and organic synthesis. It also may enter the environment via military screening smokes, primarily hexachloroethane/zinc oxide smokes, where the principle end product of combustion is zinc chloride.

When hexachloroethane (HCE) smoke, containing approximately 47.5% zinc oxide, is detonated, the principle component of the reaction product is zinc chloride. Cullumbine (1957), as cited in Hill et al. (1978), estimated that for every 100 g of HCE smoke mixture used, approximately 40 g of zinc chloride is released. Complete combustion of a typical HCE smoke pot, with an HCE charge capacity of 13.6 kg would generate approximately 545 g of zinc chloride. Helm et al. (1971), as described by Heimburger (1977), reported a concentration in air of 4 g zinc chloride/m^3 and 0.1 g ZnO/m^3 following detonation of a smoke flair.

Under conditions of high humidity, the highly deliquescent zinc chloride, with a particle size of approximately 0.1 microns, reacts with water droplets to form highly acidic, highly caustic zinc compounds with a particle size of up to 3 microns. The reaction products are known as zinc oxychlorides. Further hydrolysis can result in the formation of zinc hydroxide and hydrochloric acid (Heimburger, 1977).

When smoke is generated in a closed environment, under conditions of low humidity, the zinc chloride particles remain and may be inhaled, passing deep into the respiratory passages. It is here that they react with the moisture in the lungs to produce the highly corrosive products responsible for the severe damage seen after inhalation exposure (Heimberger, 1977).

As a part of a risk analysis for exposure to high concentrations of zinc chloride, air samples were collected following the burning of M5, HCE smoke pots under controlled conditions Stocum and Hamilton (1976). Analysis of the particles collected on membrane filters indicated a geometric mean concentration of 1.1 g/m^3. A maximum concentration of 8.5 g/m^3 was calculated for a 12 minute emission time.

When zinc chloride comes into contact with water, it dissociates to its ionic form and combines with substances in the water to form various hydroxides as well as insoluble precipitates with other ions (Hill et al., 1978).

B. Other Zinc Compounds

Zinc is a naturally occurring element found in the earth's crust at an average concentration of 123 ppm (mg/kg) (Weast, 1987). The zinc concentration averages about 70 ppm (mg/kg) in most rock-forming minerals. The zinc content

in soil is highly variable, averaging about 54 ppm (mg/kg); it is generally higher near industrial locations or highways owing to emissions and tire wear.

Zinc concentration in sea water averages about 8 µg/L; fresh water has varying amounts of zinc but averages about 64 µg/L (NRC, 1979). The highest mean value for dissolved zinc was found in the Lake Erie basin at a level of 205 µg/L while the lowest mean of 16 µg/L was recorded in the California basin. While it is present at only trace levels in most surface and ground waters, it has been detected at levels as high as 50 mg/L in mining areas (Hill et al., 1978).In natural waters, zinc can be found in several chemical forms (e.g., as simple hydrated ions, as inorganic complexes or as organometallic complexes) (Cotton and Wilkinson, 1972).

Zinc occurs chiefly as the minerals sphalerite (ZnS), smithsonite ($ZnCO_3$), willemite (Zn_2CrO_4) and zincite (ZnO); it also replaces magnesium in silicate minerals to some extent and is found in most igneous rock (Cotton and Wilkinson, 1972).

Zinc is ubiquitous in all living cells, is a constituent of over 200 metalloenzymes and is involved in most major metabolic pathways (NAS, 1989; McClain et al., 1985; Prasad, 1985).

Meats, fish and poultry are the richest sources of zinc in foods, and they contribute 40-50% of the total daily intake of zinc to the diets of older children and adults. Dairy products and grains are also good sources of zinc. They each contribute 10-13% of the zinc in the adult diet. Dairy products play a more important role as sources of zinc in the diets of young children (Pennington and Young, 1991).

The National Research Council (1989) estimates that, in the United States, typical mixed diets furnish between 10 and 15 mg zinc/day. A comprehensive analysis, based on 3-day intake records of 150 individuals showed that the average daily zinc intake from food was 12 ± 5.5 mg/day for men and 9.5 ± 0.8 mg/day for women (Bowerman and Harrill, 1983). Women in the 19- to 50-year-old groups had the lowest average zinc intake with only 8.7 ± 4.5 mg/day. Spencer and Gatza (1980) found an average daily intake of 12.5 mg/day from the analysis of institutional metabolic diets over a 10-year period. In another analysis of dietary food composites from 22 subjects, average zinc intake was 8.6 ± 0.5 mg/day (Holden and Wolf, 1979).

During the period from 1982 to 1989, the average zinc intake for United States adults (as determined by the Food and Drug Administration Total Diet Study) was 9-16 mg/day (Pennington and Young, 1991). The zinc in the diet was not sufficient to meet the Recommended Dietary Allowance (RDA) for young children, adolescent females or adult females. In addition, the zinc intake from the diet was below the RDA for elderly males and females (Pennington and Young, 1991). Recent surveys of the American population indicate that there is no widespread occurrence of zinc deficiency in individuals consuming a balanced diet selected from the available food supply, although zinc intakes are lower than recommended, particularly in women (Pilch, 1989).

The average zinc concentration in tap water across the United States is 0.245 mg/L (Greathouse and Craun, 1978). The highest mean value reported for tap water zinc concentrations from standing water in galvanized pipes is 1.979 mg/L (Sharrett et al., 1982).

IV. ENVIRONMENTAL FATE

A. Zinc Chloride

Ignition of zinc-containing smokes results in the dispersion of additional zinc chloride into the environment. Hydrolysis is the main transformation process for zinc chloride in both air and water. In air, zinc chloride hydrolyses with the available moisture to form hydrochloric acid and zinc oxychlorides ($ZnCl_2 \cdot ZnO$). In high-temperature hydrolysis studies, zinc chloride had a half-life of 17,000 minutes in the aerosol state. Similar studies were not available for environmental temperatures at various relative humidities (Spanggord et al., 1985).

Once introduced into the water, zinc chloride is rapidly transformed by hydrolysis to zinc ions (Zn^{++}) and chloride ions (Cl^{-}). The ionic zinc may then react to form such chemical species as $Zn(OH)^{+}$, $Zn(OH)^{+3}$ and $Zn(OH)_2$. In very basic solutions, zincates may form. The zinc ion also forms insoluble precipitates with carbonates, sulfides, phosphates and silicates present, resulting in the immobilization of zinc in the water (Hill et al., 1978).

In soil, adsorption plays a major role. The fate of zinc in soil is highly dependent upon pH and oxygen availability as well as various physical characteristics of soil. Zinc chloride is not likely to be affected by photolysis, vaporization, or biotransformation processes.

B. Elemental and Ionic Zinc

Zinc, as a trace element, is carried by prevailing winds from natural and anthropogenic sources to remote marine environments. The transport of zinc in the aquatic environment is controlled by the speciation of the ion. In most unpolluted waters, zinc exists mainly as a divalent cation and is easily absorbed by hydrous metal oxides and clay minerals. In polluted areas, organic material has a significant effect on the chemical form of zinc. Precipitation of zinc compounds appears to be important only in reducing environments or highly polluted waters. Photolysis and volatilization of zinc are not likely in an aquatic environment (Callahan et al., 1979).

Concentrations of zinc in suspended and bed sediments always exceed concentrations in ambient waters (Angino et al., 1976), and an inverse correlation exists between zinc concentration in the sediment and sediment grain size (Perhac, 1974b; Pita and Hyne, 1975), which implies that sorption, rather than precipitation, is responsible for this phenomenon.

The composition of the dissolved and suspended solids load has an important effect on the mode of transport of zinc in ambient water. In cases where the solids are primarily dissolved, most of the zinc in ambient water is transported in solution as the hydrated cation or complex species (Perhac, 1972, 1974a; DeGrott and Allersma, 1975). In cases where suspended solids make up a high proportion of the total solids load, most of the zinc transported will be sorbed to the suspended and colloidal particles (Kubota et al., 1974; Steele and Wagner, 1975). Residence in impoundments reduces the concentration of dissolved zinc, apparently due to scavenging by suspended solids and subsequent deposition (Pita and Hyne, 1975; Perhac, 1974b).

The tendency of zinc to be adsorbed is also affected by pH, salinity, and the concentration of complexing ligands. In a study of heavy metal adsorption by two oxides and two soils, zinc was completely removed from solution when the pH exceeded 7; below pH 6, little or no zinc was adsorbed (Huang et al., 1977). Helz et al. (1975) found that zinc was desorbed from sediments as salinity increased; this, apparently, was due to displacement of the adsorbed zinc ions by alkali and alkaline earth cations which are abundant in brackish and saline waters. Addition of inorganic complexing ligands enhanced the affinity adsorption of zinc (Huang et al., 1977).

Colloidal and suspended organic matter also adsorb zinc. Rashid (1974) reported that about 26.1 mg of zinc were adsorbed per gram of sedimentary organic matter added to a solution of zinc.

Holmes (1977) concluded that formation of zinc sulfide controls the mobility of zinc in Corpus Christi Harbor (an estuarine system). Seasonal fluctuations in dissolved zinc levels were attributed to variations in reduction-oxidation potential. In studying an impoundment polluted with zinc (400 µg/L) introduced by the dumping of mine wastes, Weatherley and Dawson (1973) found that zinc was precipitated as an amorphous colloidal deposit of basic carbonates and sulfates. Under oxidizing conditions, precipitation of these zinc compounds is probably important only where high concentrations of zinc exist.

Zinc is ubiquitous in soil with levels ranging from 10-300 mg/kg (Hill et al., 1978). In general, Zn^{++} is retained in the top few centimeters (5-10 cm). Its movement through soil is affected by various factors, with movement facilitated by anaerobic conditions and in acidic soil.

Adsorption of zinc ions in the soil is facilitated by the presence of hydrous oxides of iron, aluminum and manganese, giving rise to hydrous-oxide zinc compounds. Adsorption is also facilitated in finely divided soils such as silt, clays and colloids. Zinc has been shown to precipitate near the surface in soils containing calcium carbonate or lime or in soils high in organic content. Zinc-soil complexes also are formed. At pH 7.7 and below, Zn^{++} is found in equilibrium with soil zinc while above that pH, $Zn(OH)_2$ predominates (Hill et al., 1978). Addition of a digested sewage sludge containing 4,300 mg/kg of zinc to soil during eight growing seasons showed that 46% of the applied zinc was retained in the soil (Hinesly et al., 1977).

From its natural presence in water and soil, zinc has been shown to accumulate in biological species. Application of a fertilizer containing 129 mg/kg of zinc resulted in accumulation of the zinc in grains, leaves and legumes but not in roots, squashes and tomatoes (Schroeder et al., 1967).

Hill et al. (1978) reported that marine species accumulate zinc, with tissue levels measured at 6-1,500 mg/kg (EPA, 1976). Application of 10 millicurie of ^{65}zinc by spraying a pond surface resulted in a rapid movement of the zinc from water to sediments to organisms with 36% in sediment, 5% in biota and the remaining 59%, mainly as suspended material, in water after the first 24 hours (Duke, 1967). Maximum levels were reached in organisms after 2 days, while 0.6% was found in biota and 99.4% in sediment after 100 days.

Wildlife and domestic animals also accumulate zinc, mainly in muscle. Over a 45-year period, the human body accumulates zinc to levels of 30-60 mg

(Schroeder et al., 1967). As the infant body contains little or no zinc, an accumulation rate of 0.67-1.3 mg/year has been calculated.

V. TOXICOKINETICS

The toxicokinetics of zinc have been well studied in animals and humans. Zinc is absorbed moderately well following oral intake. Absorption through the skin is minimal while data on absorption following inhalation of particulate zinc is limited. Radiolabeled zinc was mainly distributed to the intestines, prostate, liver and kidney with kidney levels remaining highest after intravenous administration. Metallothionein plays an important role in regulating zinc homeostasis. Excretion is mainly through the feces.

A. Absorption

1. Zinc Chloride

Payton et al. (1982) reported on a method for determining human zinc absorption following oral administration. Intestinal absorption was determined from the ratio of ^{65}[Zn]-zinc chloride and a non-absorbed radioactive marker, ^{51}[Cr]-chromic chloride. The marker had no effect on zinc absorption and had a intestinal transit time similar to that of zinc. Absorption was measured by both whole body and stool counting. Retention was determined from the proportion of the dose remaining in the body 7-10 days after administration. Doses were administered to 17 healthy adult volunteers (sex not specified) ranging in age from 18-46 years. The individuals were fasted overnight prior to dosing. An initial dose-response study indicated that approximately 55% of the administered ^{65}zinc chloride was absorbed at doses of 18, 45 and 90 µmol of zinc. Absorption was reduced with increasing dose, indicating that zinc absorption is saturable. At a test dose of 900 µmol, only 25% of ^{65}Zn was absorbed.

Further studies were conducted by Payton et al. (1982) using a dose of 92 µmol of ^{65}zinc with the chromium marker. Results of zinc absorption, as measured by dual isotope stool counting or whole body counting, and zinc body retention, as measured by whole body counting 7-10 days after dosing, were comparable. Among 16 healthy individuals, average initial absorption as measured by body counting was 48% and by stool counting 50%, with a close correlation between individual results by the two methods. No significant differences were found between sexes. Absorption values corresponded closely with the predicted mean absorption of 48%, corrected for endogenous excretion. Similar studies were conducted in ostomy patients, patients with celiac disease in relapse and in one patient with radiation injury of both small and large intestine. There was no difference in absorption among the ostomy patients but those with intestinal malabsorption showed a significant decrease in absorption (average 30%). This finding indicated the importance of the proximal intestinal mucosa in the absorption of inorganic zinc.

Hill et al. (1978) reviewed the absorption studies of zinc chloride in animal species and concluded that there were conflicting results. In a study by Feaster et al. (1955), only 5% of a single tracer dose was absorbed in adult female rats over 24 hours. In contrast, Methfessel and Spencer (1973) reported that 25% of a dose of labeled ^{65}zinc chloride was absorbed within 30 minutes of oral intubation. There was little increase in zinc uptake from the gastrointestinal tract over the next 6 hours.

Four healthy men were given three different oral doses of tracer ^{70}zinc (expressed as mg ^{70}zinc chloride) at weekly intervals against a background of

15 mg/day dietary zinc. Absorption was 81% from a 4.52-mg tracer dose, 77% from a 6.47-mg tracer dose, and 61% from a 24.52-mg tracer dose. For a 70 kg man the doses were approximately 0.06 mg/kg, 0.09 mg/kg and 0.35 mg/kg respectively. A linear increase in absorption of dietary zinc within the range 4.52 to 24.52 mg zinc and a decrease in fractional absorption with larger zinc doses were observed. A reduction in dietary zinc from 15 to about 1.6 mg resulted in a significant ($p<0.005$) increase in fractional zinc absorption of the fixed tracer dose (1.19 mg) from 81 to 92%. Thus, the dose of zinc has a significant effect on its fractional absorption, and dietary restriction of zinc results in prompt increase of zinc absorption (Istfan et al., 1983).

In a study by Methfessel and Spencer (1973), ^{65}zinc as the chloride salt was instilled in vivo into ligated sacs formed from the duodenal portion of the small intestines of rats. The absorption of ^{65}zinc was significantly greater from the duodenum than from the more distal portions of the small intestine. The mid jejunum and ileum exhibited similar absorption; only minimal amounts were absorbed from the stomach, cecum and colon.

Uptake of ^{65}zinc from labeled zinc chloride was measured in four 10-cm consecutive intestinal segments of weanling pigs starting 1 cm distal to the pylorus. Data from a continuous-flow in vitro perfusion system for noneverted sacs, revealed no significant differences attributable to gut segment position (Hill et al., 1987).

Skog and Wahlberg (1964), indicated that absorption following percutaneous application was minimal when solutions of 0.08-4.87 M aqueous ^{65}zinc chloride were applied to the skin of guinea pigs. In these studies less than 1% of the administered dose was absorbed over 5 hours.

Absorption following inhalation of particulate zinc chloride by five soldiers from a smoke ammunition bomb was indicated by a slow (rate not reported) increase in plasma zinc levels following exposure for two minutes or less (Hjortso et al., 1988). Treatment with acetylcysteine, a heavy metal chelating agent, by either intravenous infusion or nebulization resulted in increased urinary zinc excretion.

2. Other Zinc Compounds

The absorption of zinc is similar in humans and other mammalian species and is affected by the amount of zinc ingested, physiological need, the fiber content of the diet, and the ratio of dietary zinc to other divalent cations (Davies and Nightingale, 1975; Greger, 1992; NRC, 1989; Seal and Heaton, 1983; Solomons and Jacob, 1981; Turnlund et al., 1984; U.S. EPA, 1987).

Numerous studies indicate that zinc absorption is regulated, in part, by the zinc content in the intestinal mucosa, which, in turn, is regulated by the zinc content of plasma (Evans et al., 1973; Ansari et al., 1976; Weigand and Kirchgessner, 1978; Cousins, 1985). The zinc absorption process includes both passive diffusion and a carrier-mediated process (Tacnet et al., 1990). A cysteine-rich low molecular weight protein has been identified in the intestinal mucosa which may be responsible for the carrier-mediated process (Hempe and Cousins, 1991). This protein bound nearly 50% the radiolabeled zinc entering the intestinal cells from the lumen in ligated loops of the small intestine of anesthetized rats when the zinc concentration was 5 µM, but

only 25% of the label when the concentration was 300 μM. This suggests that the cysteine-rich protein has a limited binding capacity for zinc and is saturated when the intestinal concentration of zinc is high.

The zinc in animal products has a higher coefficient of absorption than that from vegetable products. Phytates (inositol hexaphosphate) present in whole grains adversely affect the bioavailability of zinc by reducing its absorption (Mason et al., 1990; Sandstead et al., 1990). The concentrations of iron and calcium in the diet can also decrease zinc absorption (Dawson et al., 1989; Sandstead et al., 1990; Solomons, 1982).

The typical American diet favors zinc absorption since it includes a high consumption of meat and dairy products. Zinc absorption from different diets (e.g., vegetarian, high fiber) can be considerably lower. Many studies report zinc absorption of only 20-30% (Sanstead, 1973). Recent guidelines use an absorption coefficient of 20% to account for the lower absorption of zinc from fiber-rich diets (NRC, 1989).

Studies using everted sacs of rat duodenum and ileum revealed that zinc uptake was greater in the duodenum than the ileum and was influenced by the pH of the medium. Reducing the pH of the incubation medium from 7.3 to 6.4 significantly decreased zinc uptake ($p<0.001$) by the duodenal sacs from 23.4 ± 0.9 to 15.2 ± 1.5 μg/g dry tissue (mean ± SE) after 30 minutes of incubation. Increasing the pH from 7.3 to 8.3 also significantly decreased the uptake of zinc ($p<0.001$) by the ileal sacs from 13.0 ± 0.5 to 8.6 ± 1.1 μg/g dry tissue (mean ± SE) per 30 minutes of incubation. Zinc uptake from salts varied in the following order: zinc acetate>zinc sulfate>zinc chloride>zinc phosphate> zinc citrate. Addition of aspartic acid and/or histidine to zinc chloride increased the uptake, and addition of galactose and lactose decreased it (Seal and Heaton, 1983).

B. Distribution

1. Zinc Chloride

Upon post-mortem examination of two victims (death from respiratory complications) of inhalation exposure to a zinc chloride smoke bomb, Hjortso et al. (1988) reported that the striated muscle showed elevated zinc levels when compared to tissue of non-zinc chloride exposed trauma victims. Only one of the victims showed elevated levels of zinc in lung tissue. All other tissue zinc levels were within normal limits.

Average total body retention of ^{65}zinc administered orally as zinc chloride was measured after an overnight fast in 50 patients with taste and smell dysfunction (Aamodt et al., 1986). There were no significant differences ($p>0.25$) in zinc retention between the first phase of the experiment (days 1-21) and the second "placebo" phase of the experiment (days 22-336). During the third phase of the experiment (112-440 days, mean 307 days), 14 patients were continued on the placebo and 36 patients received zinc sulfate (100 mg Zn^{++}/day). The latter group demonstrated an accelerated loss of total body zinc (shortened biological half-time of 235 ± 8 days; mean ± SEM), which was significantly different ($p<0.001$) from the placebo-treated group (biological half-time of 384 ± 8 days; mean ± SEM). Accelerated loss of ^{65}zinc from the thigh muscle was apparent immediately; however, loss from the liver began

after a mean delay of 107 days. There was no apparent effect on loss of ^{65}zinc activity from red blood cells.

Feaster et al. (1955) reported that the highest concentrations of radioactivity, were recovered in the kidney, liver and pancreas, 4 days following the oral administration of a single tracer dose of ^{65}zinc chloride to female rats. Relatively little radioactivity was recovered from the muscle, hide and hair, and bones.

Six hours after oral administration of 0.1 µCi of ^{65}zinc as zinc chloride to 30 Wistar rats (sex not reported), highest levels of radioactivity were found in the small intestine followed by the kidney, liver and large intestine. Smaller amounts were found in the lungs and spleen. At 14 days after administration, highest levels of radioactivity could be found in the hair, testicles, liver and large intestines (Kossakowski and Grosicki, 1983).

Following oral intubation of ^{65}zinc (1 µCi of ^{65}zinc chloride, specific activity 0.81 µCi/mg zinc) in the intact rat ingesting a diet containing 40 ppm zinc, maximum radioactivity (0.09% of the administered dose) was attained in the whole blood at 30 minutes (Methfessel and Spencer, 1973). The activity decreased to about 0.045% at 1 hour and to 0.01% at 24 hours. Liver and pancreas both had a ^{65}zinc concentration of 0.1% (percent of dose/g wet tissue) at 15 minutes which increased to 0.6% at 8 hours and decreased to 0.3 and 0.2%, respectively, at 24 hours. The uptake of ^{65}zinc in femur and muscle was generally low (0.01-0.17% over 24 hours).

Following intravenous administration of a single dose of ^{65}zinc (as zinc chloride) in mice, the liver contained 25%, and the pancreas, kidneys, and small intestines contained about 1.7-2.4% of the administered label at 2-3 hours post-dosing (Sheline et al., 1943a). Levels in bone tissue increased from approximately 4-10% of the ^{65}zinc dose/g tissue during the first week post-dosing.

In two dogs (sex not reported) administered a single IV dose of ^{65}zinc (as zinc chloride), radiolabeled-zinc levels in erythrocytes during the first 24 hours post-dosing ranged from 1.9 to 3.2% of recovered radioactivity and were about 4% at the end of 1 week (Sheline et al., 1943a). Approximately 9.5% of the radiolabeled-zinc appeared in skeletal muscles 3-8 hours post-dosing. The total radioactivity recovered 1 day after dosing was 13%; at 4 days, 35%; and at 7 days, 26%.

The tissue uptake of radiolabeled 15 µCi ^{65}zinc (as the chloride salt) was determined in adult male Wistar rats following a bolus intraperitoneal injection (Pullen et al., 1990). For each of the 12 organs evaluated there was a straight line relationship of uptake with time. The regression coefficients for the uptake plots were calculated; the liver displayed the greatest uptake of zinc (2.14 E-2 mL/min/g), followed by the kidney (1.30), pancreas (1.25), spleen (1.03), ileum (0.91), lung (0.52), heart (0.43), bone (0.42), testis (0.15), blood cells (0.12), muscle (0.06) and brain (0.05), all in units of E-2 mL/min/g. Additional data on zinc uptake by the brain indicate that the blood-brain barrier is minimally permeable to zinc.

Eight hours following intravenous administration of ^{65}zinc chloride to rabbits, tissue levels were highest in the liver, intestine and kidney with levels reported as being ≥ 10%/g in tissue (Lorber et al., 1970). Sheline et

al. (1943b) injected a total of 31 mice and 5 days (sex and strain not reported for either species) with an unspecified dose of ^{65}zinc chloride. In mice, at 8 hours post-dosing, 17% of the dose was recovered from the liver, while levels in the small intestine, colon, kidney, spleen and stomach were between 10% and 1%. Percentage recovery from the liver remained high (3.3%) up to 170 hours after injection. In dogs, levels in the liver (34%), small intestine (10%) and skeletal muscle (9.6%) were highest followed by kidneys, pancreas, stomach, colon and heart (≤3.9%) at 8 hours after treatment. As in mice, the liver levels of radioactivity remained elevated (≥1%) in the 170 hour assay.

2. Other Zinc Compounds

The body of a normal human male weighing 70 kg contains approximately 1.4 to 2.3 g of zinc. About 20% of this total is thought to be present in the skin. The highest concentrations of zinc are found in the prostate (100 µg/g wet tissue) and semen (100-350 µg/L). Typical zinc concentrations (expressed as µg/g fresh tissue) in other human tissues are: kidney, 55; liver, 55; muscle, 54; heart, 33; pancreas, 29; spleen, 21; testes, 17; lung, 15; brain, 14; and adrenal gland, 12 (U.S. EPA, 1987).

About 98% of serum zinc is bound to proteins (85% to albumin; most of the remainder to α-2-macroglobulin). Diffusible zinc in blood is associated with albumin and amino acids and not with α-2 macroglobulin (U.S. EPA, 1987). Normal human serum zinc values are 75-120 µg/dL (Monsen, 1987) and are not particularly valuable as indicators of zinc status (Grider et al., 1990; King, 1986).

Zinc is present in erythrocytes (92.4% as cofactor for carbonic anhydrase isoenzymes and superoxide dismutase), leukocytes (mostly as zinc metalloprotein), and platelets (U.S. EPA, 1987).

Dietary supplementation of 600 ppm zinc as zinc oxide (a high, but not toxic, level) in young Cherokee S-D albino male rats (9/treatment group), for periods of 7-42 days, produced no change in the zinc levels of the tibia, liver, kidneys, small intestines (first 15 cm), heart, muscle (semi-tendinous) and whole blood (Ansari et al., 1975). However, when a single gavage dose of labeled ^{65}zinc chloride in acetate buffer (4 µCi) was administered along with the supplement 7 days prior to sacrifice, label retention of the tissues declined sharply in direct proportion to the duration of exposure in rats that had received the supplement for periods of from 7 to 21 days. The decrease in the level of label in the tissues of the zinc-supplemented animals indicates that the turnover of body zinc stores increases when the zinc load increases. There was no significant difference in the label retention in the animals given the supplement for 21 or 42 days, suggesting that there are limits to the body's ability to homeostatically adapt to continued exposure to excess zinc.

In a different study, varying dietary levels of zinc were fed to rats for 21 days (Ansari et al., 1976). Zinc (as zinc oxide) was added to the diet at levels of 1,200-8,400 ppm (in 1,200 ppm increments) for 21 days. There was an increase ($p<0.05$) in the levels of zinc in the liver, kidney and tibia with additions of 1,200 and 2,400 ppm to the diet. The tissue levels of zinc remained relatively constant for the 3,660, 4,800, 6,000 and 7,200 ppm

supplements but increased again with the 8,400 ppm supplement. Zinc levels in the muscle and heart were unaffected by any dietary level of zinc.

After 14 days, the rats were administered a single dose of labeled ^{65}zinc as the chloride salt (29.8 µCi) 7 days before sacrifice (Ansari et al., 1976). The label retention in all tissues was dramatically reduced by one to two orders of magnitude in the animals receiving 1,200 ppm supplement as compared to the controls, indicating that the animals increased the metabolic turnover of zinc in response to the increased zinc intake. However, the presence of additional zinc in the diet (up to 8,400 ppm) did not cause any additional change in label retention. In contrast to the soft tissues, the zinc label in bone increased when supplemental zinc was increased from 3,600 to 6,000 ppm and remained fairly constant with still higher intakes. These results indicate homeostatic adaptations in zinc turnover and absorption accompany increases in dietary zinc to prevent the accumulation of zinc in the tissues. Decreased absorption and increased turnover appear to regulate the body load with dietary zinc concentrations of up to 1,200 ppm; decreased absorption is more important than changes in turnover at dietary intakes higher than 1,200 ppm.

C. Metabolism

Zinc is an essential trace nutrient and is a cofactor for the function of as many as 200 enzymes including DNA and RNA polymerase, carbonic anhydrase, carboxypeptidase, aminopeptidase and superoxide dismutase (NAS, 1989). The essentiality of zinc in the human diet was recognized as the result of a series of studies in which inadequate dietary zinc was determined to be the cause of retarded growth and development of children in Iran, Egypt and Australia (Holt et al., 1980; Prasad, 1991). In human and animal research, adverse effects associated with inadequate dietary zinc include lethargy, impaired taste acuity, impaired wound healing, delayed gonadal development, abnormal dark adaptation, impaired immune response and dermatitis (Abernathy et al., 1991; Prasad, 1991).

The protein metallothionein plays an important role in regulating zinc homeostasis. This low molecular weight protein is found in the liver, kidneys, intestines, erythrocytes and other tissues. It has binding sites for cadmium, copper, mercury and zinc. Nearly one third of the 61 to 62 amino acids in metallothionein are cysteines. Metallothionein synthesis is induced by zinc exposure, stress, endotoxins, steroid hormones and interleukin-1 (Nutrition Reviews, 1989). Metallothionein is believed to act as a storage protein for zinc and thereby help to maintain homeostasis.

D. Excretion

1. Zinc Chloride

Richmond et al. (1962) reported an average biological half life of 154 days in four human subjects following a single oral dose of 0.6-1.0 µCi of ^{65}zinc chloride. The range was 149-161 days.

Sheline et al. (1943a) reported that mice intravenously injected with radiolabeled zinc chloride (dose not specified) excreted over 50% of the dose via the gastrointestinal (GI) tract. Approximately 20% of the dose was found in the feces within the first 10 hours. In contrast, urinary excretion

amounted to 2% of the dose over 170 hours of recovery. In dogs which also were administered ^{65}zinc chloride (dose not specified), excretion in the feces was less, with only 25% of the dose recovered over a 15 day period. Less than 5% of the dose was excreted in the urine.

After intravenous administration of ^{65}zinc chloride (dose not specified) to male Wistar rats, Barrowman et al. (1973) reported that the feces was the main route of excretion with the bile involved in this process. Over a period of 48 hours, 4% of the administered dose was recovered in the bile, largely associated with a low molecular weight protein and with bile pigment.

Rats receiving a single intravenous injection of ^{65}zinc chloride (0.012 or 0.020 mM zinc/kg) excreted 31-42% of the radioactivity in the feces within 75-92 hours of injection (Bruner, 1950). In mice, after a single IV injection (0.33-1.6 µg ^{65}zinc chloride), more than 50% of the ^{65}zinc dose was present in the feces and 20% was present in the urine at the end of a 170-hour observation period. Dogs administered a single IV injection of ^{65}zinc (5.7 or 6.5 µg ^{65}zinc chloride) excreted 25% of the radioactivity in the feces and less than 5% in the urine over a 15-day observation period (Sheline et al., 1943b).

2. Other Zinc Compounds

In humans and other mammalian laboratory species, fecal excretion is the predominant route of zinc loss (as much as 70-80% of the ingested amount), and urinary excretion is a relatively insignificant route (1-2% of the ingested amount) (U.S. EPA, 1987). A portion of the zinc excreted with the fecal matter represents absorbed zinc that is lost from the body with the bile (Wastney et al., 1991).

In one study of six healthy adult human males fed conventional foods, five were able to maintain zinc balance in the tissue (equivalence between dietary zinc and total excretory zinc) at an intake of as little as 5.5 mg/day (King, 1986). Balance apparently was achieved by a decrease in the fecal excretion of zinc which may have resulted from either an increase in zinc absorption and/or a decrease in the zinc lost in the gastrointestinal secretions.

Following dietary supplementation of rats with zinc (as zinc oxide) at 600 ppm for 7-42 days (Ansari et al., 1975) or at 1,200-8,400 ppm for 21 days (Ansari et al., 1976) and intubation with an oral tracer dose of ^{65}zinc (4 µCi ^{65}zinc chloride, specific activity 2.1 µCi/mg zinc), there was a linear increase in fecal excretion of stable zinc in proportion to the dietary intake. The fecal excretion of the labeled zinc increased as concentrations increased to 1,200 ppm and then remained relatively constant with the higher supplemental doses.

Rats receiving the same amounts of different zinc salts in their diets (53.2 ppm of either zinc chloride, zinc sulfate, zinc phosphate or zinc citrate) over a 4-day period, excreted similar amounts of fecal zinc (87.0-98.1% of intake) and urinary zinc (1.43-2.04% of intake) (Seal and Heaton, 1983). Balance studies showed no differences in fecal excretion, total excretion or retention of zinc among rats receiving diets containing different forms of zinc.

VI. HEALTH EFFECTS

A. Health Effects in Humans

Following acute oral exposures of humans to high doses of zinc, symptoms including vomiting, diarrhea, lethargy, and irritation of the mouth, throat and stomach may occur. Acute symptoms of zinc toxicity from exposure via inhalation include dyspnea, chest constriction, retrosternal and epigastric pain, hoarseness, stridor, cough, lacrimation, expectoration and an occasional hemoptysis. Pale grey cyanosis usually develops, pulse is elevated, fever is present and bronchopneumonia can develop. Edema is widespread. Death is usually due to respiratory insufficiency. Effects are related to the hygroscopic nature of the inhaled zinc particles which combine with moisture in the lungs to form caustic substances. Zinc chloride is corrosive to skin and mucous membranes. Oral exposures to zinc acetate for longer periods of time (6-12 weeks) were shown to reduce serum erythrocyte superoxide dismutuse (E-SOD) and ceruloplasmin (biomarkers of copper status) as well as HDL levels.

All of the reports of health effects in humans are based upon studies with small numbers of subjects. Therefore, they may not reflect the responses of the general population because of variabilities due to factors such as sex, age, race, etc.

1. Short-Term Exposure

a. Zinc Chloride

Data concerning the effects of zinc chloride in humans after short-term oral exposure are limited to a few case reports. These are described below.

In 1981, Potter reported on a single case of ingestion of 4 oz of an acid soldering flux containing zinc chloride (11% as measured by atomic absorption spectrophotometry) by a 28-month old child weighing 13.1 kg (approximately 1,000 mg/kg). The child vomited twice within 5-10 minutes, before admission to a hospital for emergency treatment. Subsequent vomitus contained Hematest-positive material. Although the child was lethargic, no adverse effects were noted upon physical examination except for an increase in serum zinc levels at a high of 1,944 µg/dl approximately one hour after ingestion. Twelve hours after the administration of a single dose of 150 mg of calcium disodium ethylenediamine-tetra acetic acid (EDTA) in 75 mL of 1:5 normal saline, the serum zinc level was 134 µg/dl (normal values are 77-137 µg/dl). Esophagoscopy was generally normal except for some minor bleeding from mucosal abrasions. Radiologic examination of the skeleton, electrocardiographic examination of the heart and detailed neurological evaluations were all within normal limits. Two years after the incident, the condition of the child remained unremarkable. It was felt that the powerful emetic properties of the zinc chloride prevented absorption of the ingested dose thereby limiting systemic effects.

In a similar incident reported by Chobanian (1981), a 24-year old male ingested 3 oz of a solder flux containing zinc chloride (concentration not specified). Symptoms were manifested as an immediate burning of the mouth and throat and were accompanied by severe abdominal pain, nausea and vomiting. While vital signs were normal, the patient developed indications of lethargy. Abnormal laboratory findings included elevated white cell counts, blood sugar,

amylase and zinc while the serum calcium was mildly decreased. Urinalysis disclosed a microhematuria without casts or other cellular elements. Physical examination revealed erythema, edema and erosion of the pharynx and esophagus without ulceration. A mild diffuse erythema of the stomach was evident. Within 24 hours of chelation therapy serum zinc levels were normal, 50-90 µg/dl, while the microhematuria persisted over the next 72 hours with no signs of renal dysfunction. Clinical signs, in this case, were suggestive of acute pancreatitis. This is consistent with zinc in the pancreatic secretions. Pancreatic damage might account for the increased serum glucose levels encountered in this individual. The amount of zinc chloride ingested, in mg/kg, could not be determined from the available information.

Markwith (1940) reported on a single case of industrial intoxication occurring in a closed environment due to exposure to solders that contained copper and zinc chloride. Clinical symptoms included malaise, headache, chills and pain on swallowing. Physical examination revealed a reddening and loosening of the mucous membranes of the mouth and throat, followed by the membranes becoming dry and leathery until swallowing became impossible. On the 10th day following exposure, a carbuncle formed on the chin. The patient died on the 13th day with clinical signs of sepsis.

A number of studies reported toxic effects in humans following the inhalation of particulate zinc chloride smoke in military and industrial environments. Toxic symptoms mainly involved the mucous membranes of the nasopharynx and respiratory tract. Damage to the lungs was minimal, with little or no venous congestion. Symptoms associated with inhalation exposures to zinc chloride include inflammation of the respiratory tract, respiratory difficulty, bronchopneumonia, sore throat, metallic taste, cough, chest pain, fever, headache, fatigue, nausea, vomiting, edema, and necrosis and hemorrhage of mucous membranes (Evans, 1945; Milliken et al., 1963; Macauley and Mant, 1963; Hjortso et al., 1988; Matarese and Matthews, 1986; Schenker et al., 1981). Death may occur following serious exposures (Evans, 1945; Milliken et al., 1963; Macauley and Mant, 1963; Hjortso et al., 1988). Following less serious exposures, full recovery may occur within 1-6 weeks (Evans, 1945; Schenker et al., 1981). Although these studies generally did not provide quantitative information on exposure, Stocum and Hamilton (1976) analyzed the dose-response effects from several reports of inhalation injuries due to exposure to zinc chloride smoke. Based on the concentration and exposure duration, these authors categorized inhalation effects as indicated in Table VI-1.

b. Other Zinc Compounds

Data on adverse health effects in humans exposed to excessive amounts of zinc are limited. Since zinc is an essential element for human growth and nutrition, most of the available studies on humans relate to functional consequences of zinc deficiency, pharmacologic use of zinc supplements, accidental exposure (mostly to zinc fumes) in occupational settings, or cases involving suicide (Cousins, 1986; McClain et al., 1985; Prasad, 1985; Prasad et al., 1978; U.S. EPA, 1987).

King (1986) conducted a study in which dietary zinc was reduced from 16.5 to 5.5 mg/day in the diets of 6 men over an 8-week period. Several metabolic and physiological changes were observed: serum albumin, prealbumin and retinal-binding protein concentrations decreased. Also, the levels of thyroid-stimulating hormone (TSH), T_4 (thyroxine), free T_4, and the basal metabolism

Table VI-1

Categories of Effects Due to the Inhalation of Zinc Chloride Smoke[a]

Dosage[b] g-min/m^3	Effect	Grade
NA[c]	Essentially no effect, some awareness of presence	0
0.16 to 0.24	Noticeable irritation of nose, throat and chest	1
1.7 to 2.0	Marked irritation, hospitalization and treatment required	2
20	Severe irritation, chemical pneumonia, hospitalization and treatment required	3
50	Massive injury, may be fatal	4

[a] Reference: Stocum and Hamilton, 1976.
[b] Concentration x exposure time
[c] NA = not applicable

rate decreased. Fasting plasma glucose levels increased. While none of the changes were large and may not be clinically significant, the author surmised that 5.5 mg/day is probably below the amount required for good tissue status.

Short-term, high-level intake, resulting in acute gastroenteritis, can result from consuming foods improperly stored in zinc-containing vessels (NRC, 1989). It has been reported that the emetic dose of zinc is 225-450 mg in humans (Brown, 1964). Approximately 300-350 persons developed intestinal symptoms such as severe diarrhea with abdominal cramping (about 50% developed gross blood in the feces) within 24-48 hours after ingesting food which became contaminated with zinc during preparation and storage in galvanized containers (Brown, 1964). The concentration of zinc in the fecal matter collected from several subjects during the investigation of the food poisoning episode ranged from 59 to 1,200 mg/kg as compared to a normal value of 90-100 mg/kg. The available data do not present enough information for an exposure calculation.

In another episode, individuals consuming a zinc-contaminated alcoholic fruit punch developed a hot taste and dryness in the mouth, nausea, vomiting and diarrhea from 20 to 90 minutes after ingestion (Brown, 1964). In the post-acute phase, the individuals reported general discomfort and muscular pain. All of the victims recovered from the acute adverse effects within 24 hours of exposure. The zinc concentration of a 5 oz serving of the punch was 325 mg or a dose of 4.6 mg zinc/kg for a 70-kg person. The dose increased with the number of glasses of punch consumed.

Gastrointestinal distress has also been reported in individuals receiving zinc supplements (as the acetate or sulfate) of 50-150 mg/day over a period of 6 weeks to 2 years (Freeland-Graves et al., 1982; Prasad et al., 1978; Samman and Roberts, 1988).

An accidental parenteral administration of 7.4 g zinc sulfate over a 60-hour period (approximate dose 2.96 g/day or 289 mg zinc/kg/day in a 60-kg female) to a Crohn's disease patient produced hypotension, pulmonary edema, diarrhea, vomiting, jaundice, oliguria, high serum zinc (4.184 mg/100 mL; normal serum zinc is 0.075-0.124 mg/100 mL) and death (Brocks et al., 1977).

Chandra (1984) reported on the effects of administering 150 mg of dietary zinc (as the sulfate salt) twice daily (300 mg zinc/day) to 11 adult males for 6 weeks. Average dietary zinc during the supplementation period was 10.1 mg/day, based on 24-hour recall data and 11.2 mg/day in the pretest period. Thus, the daily zinc intake was 311 mg/day (or 4.4 mg/kg/day for a 70-kg male) during the supplementation period. Fasting serum cholesterol, high density lipoprotein (HDL)-cholesterol, low density lipoprotein (LDL)-cholesterol and triglycerides were measured on a biweekly basis for 6 weeks; follow-up measurement of these parameters was conducted at 2 and 10 weeks after the supplement use ended. Total lymphocytes, T-lymphocytes and B-lymphocytes also were measured. Lymphocyte activity was monitored through polymorphonuclear migration response to chemotactic phytohemagglutinin (PHA) stimulation and phagocytosis of opsonized bacteria.

Plasma zinc values increased during the supplement administration period. There was a significant decrease in serum HDL values during weeks 4 ($p<0.1$) and 6 ($p<0.01$) with a return to baseline levels at week 16 (Chandra, 1984). LDL-cholesterol levels were significantly increased ($p<0.05$) at week 6, but there were no significant changes in serum cholesterol and triglycerides.

There were no significant changes in lymphocyte counts during the period of zinc supplementation, but polymorphonuclear response to PHA stimulation (chemotactic migration) and phagocytosis were diminished (Chandra, 1984), suggesting that there was some functional impairment in immunological response which accompanied the zinc supplementation. This study indicates a Lowest-Observed-Adverse-Effect-Level (LOAEL) for zinc of 4.4 mg/kg/day.

Supplementation with 160 mg zinc (as zinc sulfate) was found to lower HDL-cholesterol values in 11 healthy males when administered over a 5-week period (Hooper et al., 1980). A control group of eight subjects received a placebo. Fasting cholesterol, HDL-cholesterol and triglycerides were determined on a weekly basis for 7 weeks and again 11 weeks after the end of supplementation. Dietary zinc levels were not measured. The total zinc intake was 176 mg/day (or 2.5 mg/kg/day for an individual with a 70-kg body mass and a dietary intake of 16 mg zinc/day). After an initial HDL increase during the first 2 weeks of supplementation, HDL levels became significantly lower than those for the controls during weeks 4 through 7 ($p=0.002$ to 0.0001) (Hooper et al., 1980). HDL levels returned to normal 11 weeks after supplementation ended. Serum cholesterol, LDL-cholesterol and triglycerides did not change significantly during the study; serum zinc levels increased during the supplementation period. Serum cholesterol values were normal. This study suggests a LOAEL of 2.5 mg/kg/day for zinc.

Groups of 15 healthy white males were administered 0, 50 or 75 mg/day zinc (as zinc gluconate) for a 12-week period (Black et al., 1988). The subjects were given instructions to avoid foods high in calcium, fiber and phytic acid, dietary constituents which have a negative impact on zinc absorption. Subjects also were told to restrict their intake of zinc- and copper-rich foods. Three-day dietary records were collected on a biweekly basis. These records indicated that the zinc intakes of the three treatment groups were 12.5, 14.0 and 9.5 mg/day, respectively. Based on the average body weights for each treatment group, the doses for diet plus supplement correspond to zinc intakes of 0.16, 0.85 and 1.10 mg/kg/day.

Biweekly fasting blood samples were collected from all subjects and analyzed for total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, zinc and copper. Urinary zinc and copper values were also determined. There was a general decline in the mean serum HDL-cholesterol for the 75 mg supplement group between weeks 6 and 12. HDL values for this group were significantly lower than those for the placebo group at weeks 6 and 12 ($p>0.05$). There was also a decline in the HDL values for the 50 mg group from weeks 8 through 12. However, this decline was not significantly different from that for the controls until the 12th week of treatment ($p\leq0.05$). Serum zinc, copper, total cholesterol, LDL-cholesterol, and triglycerides did not appear to be affected by treatment.

Samman and Roberts (1988) administered 150 mg zinc (as the sulfate salt) to a group of 21 healthy young male and 20 female volunteers in a 12-week double blind cross-over trial. The subjects were instructed not to change their lifestyle, including their diet, alcohol consumption and exercise patterns during the study. No other dietary directions were given. The subjects were seen at 3-week intervals. The duration of the zinc exposure period was 6 weeks; subjects were given a placebo for the other 6 weeks. Non-fasting blood samples were collected for determination of plasma lipoproteins (LDL, HDL, HDL_2, HDL_3) and indicators of copper status (hematocrit, ceruloplasmin,

E-SOD, Cu-Zn-SOD). There was a slight, but nonsignificant, decline in the HDL values for both males and females. There also appeared to be a shift in HDL distribution from HDL_3 to HDL_2. There was a slight nonsignificant increase in LDL levels in males after 6 weeks of supplemental zinc, but there was a significant decrease in the LDL values for females. Accordingly, the exposure to zinc appeared to have no influence on the cardiovascular risk for the male subjects and a benefit for the females. There was considerable variability in the LDL response of the females since only about 50% of the study population exhibited a decrease in LDL values; the remainder of the subjects had LDL values that remained constant or increased.

A study of HDL response to zinc in premenopausal females suggests that supplemental zinc does not appear to have the same effect on females that it has on males. Healthy adult females were given supplemental zinc doses of 0, 15, 50 and 100 mg/day zinc as zinc acetate for 60 days (Freeland-Graves, 1982). Three-day dietary records kept at weekly intervals were used to evaluate the nutrient content of the diet including values for dietary lipids, zinc (8.1-8.5 mg/day) and copper (2.6-2.7 mg/day). Fasting plasma cholesterol, HDL-cholesterol and zinc were monitored at biweekly intervals. Cholesterol values were not reported and there was no measurement of LDL values. A transitory decrease in HDL values was noted at 4 weeks only in the group receiving the 100 mg/day supplement and 8.1 mg/day zinc in the diet (diet records) (or 1.8 mg/kg/day based on a 60-kg body weight). This decrease in HDL values was not apparent at 6 and 8 weeks. Serum zinc levels were also highest in these subjects at 4 weeks.

A very slight but statistically significant ($p=0.04$) 2 mg/dL increase in HDL cholesterol was seen in a group of 22 elderly male and postmenopausal female subjects (sex ratio unknown) 8 weeks after they ceased using zinc supplements (Goodwin et al., 1985). Serum zinc values fell from 92 to 86 µg/dL during the same period. The average supplement intake was 29.1 mg/day (with a range of 17.5-52.2 mg/day). The increase in HDL values seemed to be greatest for the subjects with the highest ratings for physical activity. Although the data in this study are far from conclusive with regard to the relationship between zinc and HDL values, they do add to the weight-of-evidence which suggests that supplemental zinc can impact HDL levels.

Healthy adult males given 25 mg of zinc (as the gluconate) twice daily for a 6-week period, displayed a significant decrease ($p<0.05$) in E-SOD activity at the end of 6 weeks of exposure (Fischer et al., 1984). The decreased concentration of E-SOD is indicative, not only of a copper deficiency, but also of a diminished capacity of the cells to respond to oxidative stress. There were no differences in serum copper levels or ceruloplasmin activity in the 13 members of the supplement group as compared to the controls. Serum zinc levels were significantly increased in the supplement group after 2 weeks. Dietary zinc was not measured. The diet plus supplement intake was 66 mg/day or a LOAEL of 0.96 mg/kg/day for a 70-kg male with a dietary intake of 16 mg/day.

Almost identical results were obtained from a 10-week study of zinc supplementation in 18 healthy adult females given supplements of 50 mg zinc/day (as zinc gluconate) (Yadrick et al., 1989). E-SOD concentrations declined over the 10-week supplementation period and, at 10 weeks, were significantly different ($p<0.05$) from values during the pre-treatment period. Ceruloplasmin concentrations were not altered, but serum zinc was

significantly increased. There was also a significant decline in serum ferritin and hematocrit values at 10 weeks. However, neither ferritin nor hematocrit values were altered when iron (50 mg/day) was added to the zinc supplement which corrected the iron-zinc imbalance but not the copper-zinc imbalance. The zinc plus supplement intake for the females was 59.7 mg/day or a LOAEL of 1.0 mg/kg/day for a 60-kg female with a dietary copper intake of 9.7 mg/day.

Several indicators of a copper deficiency were noted in the 20 females administered 150 mg zinc/day for 6 weeks during a double blind placebo study (Samman and Roberts, 1988). Ceruloplasmin, E-SOD and Cu-Zn-SOD concentrations were all significantly decreased during the zinc supplement period when compared to the values during placebo administration. There was a 20% decrease in E-SOD and a 23% decrease in Cu-Zn-SOD at the end of 6 weeks. The same parameters were very slightly decreased in the males, changes were not significant.

Nine healthy men (21-27 years of age) were given daily diets containing 2.63 mg copper/day (0.13 mg from the diet and 2.5 mg from copper sulfate) and 1.8, 4.0, 6.0, 8.0, 18.5 or 20.7 mg zinc (1.8 mg from the diet and the remainder as zinc carbonate) for 1- or 2-week periods randomized over 9 weeks (Festa et al., 1985). The purpose of this protocol was to examine the effect of zinc on copper excretion and retention. The weekly mean (± SEM) plasma copper concentrations (81 ± 3.3 to 100 ± 5.8 µg/dL) remained within the normal range with all zinc doses. On two occasions, the 18.5 mg zinc/day dose was administered for 2 consecutive weeks after 1 week on a lower zinc dose (1.8-8 mg/day). In each instance, the mean fecal copper excretion was increased during the second week as compared to the first (from 1.92 mg/day to approximately 2.62 mg/day), and copper balance became more negative. This study demonstrated that feeding 18.5 mg zinc/day (an amount only 3.5 mg above the recommended dietary allowance (RDA) which is 15 mg zinc/day for adult males) resulted in elevated fecal copper excretion and reduced copper retention during a 2-week period.

Some data suggest that supplemental zinc impacts iron absorption. Crofton et al. (1989) administered solutions of 23.5 mg of ferrous iron (as the hydrated sulfate salt) either alone or combined with zinc (as the sulfate salt) (27.5 or 68.5 mg zinc) to a group of seven subjects and measured the area under the plasma time curves. The minerals were administered after an overnight fast and testing episodes were separated by 35 days. There was an incremental decrease in the area under the curve (AUC) for iron at 3 and 6 hours when the combination of zinc and iron was used. The lower zinc concentration decreased the AUC for iron by 66% at 3 hours and 72% at 6 hours; the higher dose decreased the value by 80% at 3 hours and by 90% at 6 hours.

2. Dermal/Ocular Effects

a. Zinc Chloride

Contamination of the eye with concentrated solutions of zinc chloride causes severe damage to both the cornea and the lens. In 1973, Houle and Grant reported on a case of splash injury with concentrated zinc chloride galvanizing solution (pH 3.53) to both eyes and the nasal passages of a 38-year old male. Despite extensive irrigation with water, the initial ophthalmic examination revealed a reduced visual acuity, puffy swelling of the

eyelids, pale and markedly chemotic conjunctiva and epithelial edema of the cornea. The cornea remained permanently scarred with persistent gray spots present beneath the anterior lens capsule. Prior to this injury, uncorrected visual acuity was 20/20. Two years later, visual acuity in the more severely damaged right eye was 20/200 correctable by refraction to 20/60 while the left eye was correctable to 20/30.

Examination of the nasal passages revealed whitish speckled eschar-like lesions on the anterior mucosa with complete bilateral nasal obstruction. The patient permanently lost all sense of smell from the zinc chloride injury (Houle and Grant, 1973).

Du Bray (1937) described symptoms of fatigue, anorexia, weight loss and pain in the long bones of a man exposed to aqueous zinc chloride solution by frequent and long-term immersion of the hands. Concentration of the aqueous solution was not reported.

b. Other Zinc Compounds

No information was found in the available literature regarding dermal/ocular effects in humans of other zinc compounds.

3. Long-term Exposure

a. Zinc Chloride

No information was found in the available literature regarding long-term health effects in humans of zinc chloride.

b. Other Zinc Compounds

Anemia and neutropenia developed in a 44-year-old male patient who had taken 43 mg zinc/day (as zinc gluconate) for a 2-year period (Simon et al., 1988). Serum zinc was elevated (262 µg/dL) while serum copper (15 µg/dL) and ceruloplasmin (2 µg/dL) values were low; hemoglobin (9 g/dL), hematocrit (25.7%) and white cell count (2,000/µL; 6% neutrophils) were also depressed. At 7 weeks after discontinuing the supplement, all physiological measurements of copper and zinc status returned to normal and the patient's anemia was resolved.

A 35-year-old woman with a history of gastrointestinal problems (gastric ulcers, reflux gastritis, intestinal obstruction and ulceration) was prescribed a zinc supplement for ulcers of the mouth and tongue (Hoffman et al., 1988). For a 10-month period she ingested 142-197 mg zinc/day as the sulfate salt. Although the oral ulcers responded to the zinc treatment, the patient developed a microcytic hypochromic anemia which did not respond to 6 months of iron therapy. After 10 months of the zinc therapy combined with iron for 6 months to resolve the anemia, the patient's serum copper and ceruloplasmin values were extremely low (0.15 µg/dL for copper and 0 for ceruloplasmin). (Normal is 0.75-1.45 µg/dL for copper and 22.9-43.1 mg/dL for ceruloplasmin.) The use of the zinc supplement was then discontinued and the patient was given 2 mg/day copper for 2 months. Although there was some initial increase in serum copper and ceruloplasmin, the patient's hematological parameters did not improve, and zinc excretion continued to be high. Over a 5-day period, a total dose of 10 mg copper (as the chloride

salt) was given intravenously. Within 2 weeks, ceruloplasmin increased to 19.5 mg/dL. Oral copper therapy (2 mg/day) was continued. The patient's anemia was resolved, serum copper and ceruloplasmin, and white cell count returned to normal after 5 months.

Prasad et al. (1978) reported the occurrence of a microcytic anemia and neutropenia in a sickle-cell anemia patient who had received 75-200 mg/day zinc (as either the acetate or sulfate salt) as an antisickling agent for a period of 2 years. The patient's condition was discovered when he enrolled in a study involving the use of zinc to control pain in sickle-cell patients. Based on plasma zinc and copper data which had been collected over the 2-year period, the zinc supplement caused an initial increase in plasma zinc values which gradually decreased with time; plasma copper values continuously decreased during the zinc supplementation period but increased when 1 g of copper (as copper sulfate) was added to the therapy. As a result of these findings, 13 other individuals who were taking part in a study of pain in sickle-cell patients were surveyed. Ceruloplasmin levels were below normal for seven patients. The addition of copper to the therapeutic program for these individuals resulted in normalization of the ceruloplasmin values.

B. Health Effects in Animals

In animal studies, oral LD_{50}s as well as average lethal oral doses have been reported for zinc compounds in several species. Zinc chloride causes both skin and eye irritation, and percutaneous toxicity has been demonstrated. Oral administration of zinc chloride to rats for up to 6 weeks precipitated a deficiency syndrome when combined with a synthetic diet low in pantothenic acid. Renal damage was observed in rats exposed orally to zinc for 90 days. Several studies indicate that high doses of zinc can interfere with reproductive function and can be fetotoxic. Mutagenicity and carcinogenicity studies have yielded equivocal or negative results.

1. Short-Term Exposure

a. Zinc Chloride

Limited data are available on the toxic effects of zinc chloride following acute oral exposures in animals (Table VI-2). In 1941, Woodard and Calvery, as cited in Calvery (1942), reported acute median oral lethal doses of 350 mg/kg for rats, 350 mg/kg for mice and 200 mg/kg for guinea pigs. These data suggest that the guinea pig may be slightly more sensitive to the acute toxicity of zinc chloride than other laboratory animals. In 1974, Yakuri indicated an oral LD_{50} of 502 mg/kg in male dd-K mice. Hahn and Schunk (1955) reported an average oral lethal dose of 750 mg/kg in rats and 1,000 mg/kg in rabbits (cited in Hill et al., 1978). Rats were given a single oral dose by gavage of zinc chloride in solution at 500, 750 or 1,000 mg/kg. Approximately 40% of the dosed rats died within 24 hours. Upon necropsy, perforations of the stomach or penetration into the liver tissue, as well as pyloric stenosis, were evident. Mucosal damage was less prevalent among animals dying early, but ataxia, tremor, dyspnea and a drop in body temperature were evident. A dose response was not indicated. Doses in rabbits were reported to be 250, 500 or 1,000 mg/kg. Similar effects were reported upon necropsy. Mortality rate was not specified. Domingo et al. (1988) reported oral LD_{50} values for zinc chloride of 528 mg/kg in rats and 605 mg/kg in mice.

Table VI-2

Acute Oral Studies of Zinc Chloride and Other Zinc Compounds

Chemical	Species	Effect	Dose (mg/kg)	Reference
Zinc chloride	Rat	Median lethal dose	350	Woodward and Calvery, 1941
Zinc chloride	Rat	LD_{50}	528	Domingo et al., 1988
Zinc chloride	Rat	Average lethal dose	750	Hahn and Schunk, 1955
Zinc chloride	Mouse	LD_{50}	1,000	Domingo et al., 1988
Zinc chloride	Mouse	Median lethal dose	350	Woodward and Calvery, 1941
Zinc chloride	Mouse	LD_{50}	502	Yakuri, 1974
Zinc chloride	Guinea pig	Median lethal dose	200	Woodward and Calvery, 1941
Zinc chloride	Rabbit	Average lethal dose	1,000	Hahn and Schunk, 1955
Zinc sulfate	Rat	LD_{50}	623	Domingo et al., 1988
Zinc sulfate	Rat	LD_{50}	920	Fabricio, 1974
Zinc sulfate	Mouse	LD_{50}	337	Domingo et al., 1988
Zinc acetate	Rat	LD_{50}	237	Domingo et al., 1988
Zinc acetate	Mouse	LD_{50}	86	Domingo et al., 1988
Zinc nitrate	Rat	LD_{50}	293	Domingo et al., 1988
Zinc nitrate	Mouse	LD_{50}	204	Domingo et al., 1988

Gross et al. (1941) studied the effects of orally administered zinc chloride in young female rats (40 g average weight) fed a synthetic diet. The animals were orally intubated with a vitamin-supplemented filtrate fraction low in pantothenic acid. Oral intubation with zinc chloride in cod liver oil at 4 mg/day (approximately 100 mg/kg/day for a 40-g rat) occurred at 4 hours after the vitamin supplement, 6 days/week for up to 6 weeks. Deficiency symptoms characterized by growth retardation, severe alopecia, rusting and ruffling of the fur, and crusting of the nose, chin and eyelids, were reported in ≥50% of the rats after 5 weeks of treatment. Control animals grew at a slightly suboptimal rate and had some rusting of the fur which cleared spontaneously, but developed no other symptoms. Black rats similarly treated with 5-6 mg/day of zinc chloride in olive oil developed alopecia and a severe graying of the coat as well as crusting of the nose, chin, tail and eyelids. Oral supplementation of the daily regimen with 150 µg of synthetic calcium pantothenate reversed the progress of the deficiency symptoms, even with continued intubation of the zinc chloride. Neither a No-Observed-Adverse-Effect-Level (NOAEL) nor a LOAEL could be determined.

b. Other Zinc Compounds

The acute oral LD_{50} value for zinc sulfate in rats was 920 mg/kg (Fabrizio, 1974). LD_{50} values were calculated in rats and mice (10/dose group) for four zinc salts using the Litchfield-Wilcoxon method after intragastric administration of a single dose of the salt in solution (Domingo et al., 1988). The LD_{50} for zinc (as zinc acetate dihydrate) in rats was 237 mg/kg and in mice, 86 mg/kg. The LD_{50} value for zinc nitrate hexahydrate in rats was 293 mg/kg and in mice it was 204 mg/kg. Zinc sulfate dihydrate had an LD_{50} of 623 mg/kg in rats and 337 mg/kg in mice.

Two studies on the homeostasis and tissue distribution of zinc in male Cherokee Sprague-Dawley rats weighing 100-120 g have been described (Ansari et al., 1975, 1976). In the 1975 study, one control group (seven rats) and four experimental groups (nine rats/group) were fed zinc oxide in the diet at 0 or 600 ppm for 7, 14, 21 or 42 days (Ansari et al., 1975). In the 1976 study, zinc oxide was fed to groups of 6-8 rats at 1,200, 2,400, 3,600, 4,800, 6,000, 7,200 or 8,400 ppm for 21 days (Ansari et al., 1976). There was increased excretion when zinc added to the diet was elevated above the 1,200 ppm level. This finding, as well as the observed sharp increases in stable zinc in the liver, kidney, and tibia at the highest dietary zinc intake (8,400 ppm), suggested some breakdown in zinc homeostasis. However, body weight gain and food consumption were similar in controls and zinc-treated groups, and gross clinical signs of toxicity such as skin lesions, diarrhea and muscular incoordination were not observed in any of the treated groups.

Several case studies of dogs which have swallowed zinc-containing coins or metal objects report hemolytic anemia in the affected animals (Latimer et al., 1989; Luttgen et al., 1990; Torrance and Fulton, 1987). In these cases, it is impossible to determine the dose of zinc received by the animal in order to unequivocally attribute the symptoms to zinc since zinc was not the only metal present in the objects swallowed.

2. Skin and Eye Irritation, Dermal Sensitization

a. Zinc Chloride

In a test for dermal irritation, 0.5 ml of a 10% solution of zinc chloride was applied to the skin of six male albino rabbits (Williams, 1984). The application area was prepared for testing by clipping the area free of hair. The area was covered and occluded for 24 hours prior to scoring for erythema and edema. The authors reported that zinc chloride caused severe edema and a necrotic erythema in the test area. When 0.1 ml of the 10% zinc chloride solution was instilled into the lower conjunctival sac of one eye, conjunctivitis and a moderate, penetrating corneal opacity were observed. Recovery from these effects occurred after 7-14 days.

Percutaneous administration of 2 ml of 0.239 moles of aqueous zinc chloride to a 3.1 cm^2 area of the skin of guinea pigs (mean weight 375 g) resulted in a cessation of weight gain after 1 week. Mortality was unaffected over the four-week observation period. A low absorption rate of less than 1.0 % per 5 hour exposure period was indicated (Wahlberg, 1965).

Experiments were conducted in albino rabbits (Johnstone et al., 1973) to evaluate the effects of zinc chloride on the eye with the possibility of developing more specific treatment techniques for use in human injuries. Corneal injuries were obtained by exposure for one minute to a 50% solution of zinc chloride followed by a ten second irrigation with water to remove excess test solution. One group of rabbits received no further treatment, while a second group received a 15 minute eye irrigation with either 0.9% sodium chloride or 0.05 M neutral sodium ethylenediamine-tetra acetic acid (EDTA) at one minute post-exposure. A third group received the same two treatments starting at 15 minutes after exposure to the 50% zinc chloride. Zinc content of the cornea was measured at various time intervals following injury. Neither treatment was effective in its rate of removal of zinc when compared to the untreated cornea injured by exposure. While treatment with 0.05 M EDTA did not prevent the corneal opacification seen following injury with zinc chloride, treatment within one minute following injury did result in a progressive improvement. By 2 weeks after injury the corneal opacity in the EDTA treated eyes was 1+, a marked improvement over those treated with normal saline. If treatment was delayed for 15 minutes, neither procedure resulted in improvement.

Johnstone et al. (1973) also conducted experiments with excised bovine corneal buttons. They found that zinc chloride acts as a fixative or denaturant of the cornea and that EDTA acts to some degree to reverse this denaturation when the exposure is relatively mild.

b. Other Zinc Compounds

No reports were found on the toxic effects of zinc following dermal exposure, although zinc may be absorbed across the broken and unbroken epithelial membrane (NRC, 1979).

3. Longer-Term Exposure

a. Zinc Chloride

All data on the longer-term administration of zinc chloride are associated with reproductive, developmental or carcinogenic screening studies. Details are presented in the related sections.

b. Other Zinc Compounds

Weanling COX-SP rats of both sexes (180 control rats and 40 rats/experimental group) were administered zinc phenolsulfonate (a cosmetic product) for 91 days at dietary levels of 62.5, 250 or 1,000 mg/kg/day (corresponding to calculated doses of 1, 4 and 16 mg zinc/kg/day, respectively, based on 200-g weight and 20-g/day food consumption). There was no unusual variation in food consumption, body weight gain or hematological parameters between the control and treated groups. One mg zinc/kg/day produced minor, randomly distributed variations in organ-to-body weight ratios and increased testicular fluid at the 4-week necropsy. The 4-week necropsy also revealed hydropic changes at the intermediate dose and increased vacuolar changes at the high dose in the seminiferous tubules. These effects were absent at the 8-week necropsy and at the end of the study, suggesting a temporary failure of zinc homeostasis and a subsequent endogenous repair (Elder, 1986). The influence of the organic cation on toxicity, if any, cannot be determined from the results presented in this study. Usefulness of this study for the calculation of an HA value is questionable, given the type of compound used.

Doses of 0, 47.6, 95.3 or 190.6 mg zinc/kg/day (as the acetate salt) were administered to groups of 10 female Sprague-Dawley rats in drinking water for 90 days (Llobet et al., 1988). The animals were observed daily for clinical signs, food and water consumption, and urine and fecal excretion; body weights were determined weekly. Prior to sacrifice, blood samples were collected and analyzed for biochemical indices and hematological parameters. After sacrifice, the major organs were weighed and examined histologically. There were no differences for food consumption, body weight or fecal matter production between the dose groups. The animals in the highest dose group exhibited apathy, decreased water consumption and urine production, increased serum urea and creatinine. There were no differences in hematocrit, hemoglobin or serum enzymes between groups. At the two highest dose levels there were significant increases in the zinc concentration in the liver, kidneys, heart, bone and blood but no significant differences in organ weights for the liver, kidney and heart. Lesions were seen in the kidneys of the animals exposed to the highest dose. Bowman's capsule epithelial cells were flattened and there was loss of some of the surface epithelial cells in the proximal tubules along with pyknotic nuclei in the tubular epithelial cells. There were no adverse effects associated with the 95.3 mg/kg/day dose (NOAEL), but there were some indications of renal damage at the LOAEL of 190.6 mg/kg/day.

Male and female C3H mice were provided with zinc sulfate (0.5 g/L) in distilled drinking water ad libitum for up to 12 months. The outward appearance, appetite and activity were similar to controls (Aughey et al., 1977). A total of 150 mice, including an unspecified number of controls, was used. Plasma zinc levels in the zinc-supplemented mice rose to a peak of 2.1 µg/mL at day 3 of ingestion while the control level was 1.02 µg/mL;

thereafter, a plateau with minor fluctuations was evident over the 34-day observation period. (On day 34, plasma zinc was about 1.5 µg/mL.) No significant difference in zinc content between the control and zinc-supplemented groups was observed for the liver, spleen, or skin over a 6-month observation period; no sex difference was observed with respect to zinc content of these tissues. Plasma insulin and glucose levels were unaffected by dietary zinc supplementation. However, some histological and ultrastructural changes were noticed in tissues of zinc-supplemented groups as compared to tissues of controls. Individual beta cells of the pancreas were larger than in controls. The zona fasciculata of the adrenal cortex was hypertrophied and highly positive to lipid staining at 3 months of zinc ingestion; at 6 months or more, the glomerulose and reticularis zones also gave strongly positive reactions for lipid staining. Cells of the anterior lobe of the pituitary showed morphological changes consistent with hyperactivity. It was not possible to derive a LOAEL or a NOAEL from this study for the following reasons: only one dose was used, the amount of ingested zinc could not be estimated because water spilled during drinking, intestinal absorption was uncertain, and data on body weights were unavailable. However, assuming an approximate water consumption of 10 mL/day and a mean body weight of 25 g, the daily dose in this study corresponds to about 200 mg zinc sulfate/kg/day.

4. Reproductive Effects

a. Zinc Chloride

In general, results of oral administration indicate maternal toxicity evidenced by a decrease in weight gain when zinc chloride administered by gavage at a dose of 150 mg/kg/day. In contrast, administration in the diet during reproduction revealed no toxic effects at levels up to 250 mg/kg/day.

Heller and Burke (1927) reported no toxic effects on growth, reproduction or offspring of rats following the ingestion of zinc chloride in the diet. Diets containing 0.25 or 0.5% of zinc as zinc chloride were administered during breeding and continued for one generation after the parental F_0 animals. This is equivalent to approximately 12.5 or 25.0 mg/kg/day, assuming normal dietary intake of 20 g/day for a 0.4 kg rat (Lehman, 1959). The 0.25% group consisted of 2 rats/sex; the 0.5% group had two males and 7 females. A control group of 3 males and 1 female were fed a diet that did not have added zinc. It appears that growth, mating and number of offspring were not affected by zinc chloride. The offspring, continued on the same treatment, also produced normal, vigorous offspring. No lesions or pathological conditions were seen. Tissue zinc levels (which were reported as average zinc concentration and included tissues from animals fed zinc carbonate, zinc oxide, and zinc dust) were comparable to controls. Results from this study are difficult to interpret due to its design and lack of experimental detail; therefore, a LOAEL and NOAEL are not identified. No other data were found in the available literature on the reproductive effects of exposure to zinc chloride in animals.

b. Other Zinc Compounds

Kumar (1976) orally administered 150 mg/kg/day zinc (as 2% zinc sulfate) in drinking water to 13 pregnant rats. Zinc content of the diet was 30 ppm. All animals were sacrificed on day 18 of pregnancy and examined. Eight

experimental animals showed 11 resorptions out of 116 implantations. Two control animals revealed a total of 2 resorptions out of 101 implantations. Data suggest that moderately high levels of zinc may have harmful effects on pregnancy.

In a study in which groups of 10 female Sprague-Dawley rats were maintained on diets containing 2,000 and 5,000 ppm zinc oxide for 35-38 days (from day 1 of gestation to day 14 of lactation), no malformations were observed; however, fetal mortality was noted (Ketcheson et al., 1968). A dietary level of 2,000 ppm corresponds to a calculated dose of 200 mg zinc/kg/day, assuming a body weight of 200 g and a dietary intake of 20 g/day while the 5,000 ppm dose is equivalent to 500 mg zinc/kg/day. Among the 10 litters given 2,000 ppm, 4 dead pups were observed; in the 8 litters given 5,000 ppm, 2 litters consisted entirely of dead pups (the number of dead pups in these 2 litters was not mentioned).

Dietary supplementation with zinc carbonate at 1,000, 5,000 or 10,000 ppm (corresponding to calculated doses of 100, 500 and 1,000 mg/kg/day) for 10-16 weeks resulted in an increase in stillbirths at 5,000 ppm and no reproduction at 10,000 ppm in groups of five young rats (three females and two males; strain not reported) (Sutton and Nelson, 1937). Three females on the 5,000-ppm diet had 6/11 dead pups from their first pregnancies; during their second pregnancies, all 23 pups died. No effects were observed at 1,000 ppm.

The effect of zinc on the male reproductive organs was evaluated in male Sprague-Dawley rats (number not specified) over a 3- to 6-week period (Saxena et al., 1989). The experimental animals received a diet containing 500 ppm zinc. The control animals were fed a diet with adequate zinc to support nutritional needs. The water used for both groups of animals contained 2 mg/L zinc. The total zinc intake of the experimental animals was 25 mg/kg/day. Animals were sacrificed at 3 and 6 weeks for examination of their reproductive organs. Spermatogenesis was found to be impaired in the exposed animals at 3 and 6 weeks.

No effect on embryonic mortality, male fertility, or pregnancies/ effective mating was produced by zinc chloride in the dominant lethal mutation assay using mice [F1 hybrids (CBA/X/C57BL)] and a single intraperitoneal dose (15 mg/kg) in males (Vilkina et al., 1978).

5. Developmental Effects

a. Zinc Chloride

No effects were found on reproductive parameters, but zinc chloride may be a teratogen.

Seidenberg et al. (1986) screened 55 chemicals, including zinc chloride, for possible teratogenicity, utilizing the Chernoff/Kavlock developmental toxicity screen. This method identifies developmental toxicity, including potential teratogenicity, based on growth and viability of embryonic, fetal, and postnatal mice. The screen was designed to prioritize chemicals for subsequent, more detailed, conventional study and may not be appropriate to classify chemicals as developmental toxicants.

In the zinc chloride screen, 28 timed-pregnant mice received by gavage an oral dose of 150 mg/kg/day in water on Day 8 through Day 12 of gestation. The mice were weighed on Days 7 and 13 of gestation and at one day postpartum. Dams were allowed to deliver, litters were counted and weighed on day of birth and on Day 3. Dead pups were examined for external abnormalities. Dams not delivering by Day 21 or 22 were necropsied and uteri were examined. One of the maternal animals died at this dose, and average weight gain was significantly reduced as compared to controls ($p<0.01$). Eleven litters were produced with no resorptions. No significant differences were found in the average number of neonates/litter, % survival Days 1-3, or average neonatal weight on Days 1 and 3 (Seidenberg et al., 1986).

Based on the Chernoff/Kavlok method, Seidenberg and Becker (1987) reported that zinc chloride caused a significant reduction in litter size and thus classified it as a teratogen. This parameter was not significantly different when only the litters that came to term by Day 22 of gestation were counted. Given the limitations of the method zinc chloride should be considered a potential developmental toxin. A NOAEL or LOAEL could not be determined because only one dose was tested.

One intraperitoneal study suggests that zinc chloride is teratogenic. Chang et al. (1977) injected zinc chloride intraperitoneally in mice (number not clearly specified for each dose group) in single doses of 0, 12.5, 20.5 and 25 mg/kg on days 8, 9, 10 or 11 of gestation. Dams were sacrificed on gestation day 18 (1 day prior to expected delivery). Thereafter, the number of fetuses and resorption sites was determined. Fetuses were weighed, sexed and examined for skeletal and visceral anomalies. Quantitative data on maternal toxicity and fetotoxic effects were not provided by the author for evaluation. Skeletal anomalies, including delayed ossification, were seen at dose levels of 20.5 mg/kg/day or greater beginning on gestation day 8. Ripple ribs, an unusual skeletal anomaly, first appeared when zinc chloride was given on day 9 of gestation. For the most part, the severity of the skeletal lesions was dose and time dependent. There were no significant differences in soft tissue anomalies at any dose level. Skeletal anomalies were observed at doses of 20.5 mg/kg and above but not at 12.5 mg/kg.

b. Other Zinc Compounds

Dietary zinc deficiency (0.3-100 ppm zinc carbonate) in Sprague-Dawley rats (10-20/group) and Long-Evans hooded rats (10-17/group) produced reproductive and developmental effects including testicular lesions, abnormal estrous cycles, embryotoxicity and malformed fetuses (most organ systems and the skeleton were involved) (Hurley, 1969; Hurley and Swenerton, 1966; Rogers et al., 1985; Hurley et al., 1971).

6. Genotoxicity

a. Zinc Chloride

Mutagenicity studies produced mixed results in which some cytotoxicity was indicated.

In an *in vitro* assay for detection of potential carcinogens and mutagens, Casto et al. (1979) used hamster embryo cells (HEC) to detect the ability of zinc chloride to enhance the transformation of Simian adenovirus SA7.

Enhancement occurred in only 50% of the six assays. The lowest concentration producing a positive response was 0.18 mM with a transformation ratio of 8.7 (transformation frequency (TF) of treated cells/TF of controls). Because of the 50% response, the authors reported that the results of this study were inconclusive.

Results of *in vitro* studies in normal stimulated human lymphocyte cultures did not demonstrate the mutagenic potential of zinc chloride. At a concentration of $3x10^{-5}$ M, severe chromosome aberrations were manifested as dicentric chromosomes but the incidence was not significant against controls using the chi-square analysis. At a level of $3x10^{-3}$ M, zinc chloride was cytotoxic to human lymphocytes (DeKnudt and Deminatti, 1978).

No evidence of DNA damage was observed in human white blood cells at the zinc chloride concentration of $5x10^{-5}$ M (McLean et al., 1982).

Mutagenicity tests conducted with *S. typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 indicated that zinc chloride was not mutagenic in any strain either with or without S-9 mix, although zinc chloride was toxic at the higher exposure levels (McGregor, 1980). Sokolowska and Jongen (1984) indicated that zinc chloride was not mutagenic in any strain at doses up to 5 mg/plate. In contrast, Kalinina and Polukhina (1977) indicated that zinc chloride produced frame shift mutations in the indicator strains (not specified) of *S. typhimurium* in the Ames test. The effect was measured by the ability of the chemical to induce reversions from histidine auxotrophy to prototrophy and was described as species-specific with respect to liver homogenates, with the highest mutagenic activity evident in the mouse liver.

In the *E. coli* DNA repair test, zinc chloride did not show preferential toxicity for the polymerase-deficient strain at 10 mg/plate, with or without S-9 mix (McGregor, 1980). In the *S. cerevisiae* mitotic recombinogenic activity test, zinc chloride did not show a reliable indication of toxicity to the yeast cells during the 150 minute incubation. An 18 hour incubation did result in a reduced viability at 0.75 mg/ml. In the presence of S-9 mix toxicity was severe at ≥1 mg/ml. At lower concentrations in which moderate toxicity was observed, there was no sign of an increase in recombinant frequency. In the absence of S-9 mix, results were not clear.

In an *in vivo* system using male and female F_1 hybrid mice, Vilkina et al. (1979) studied the effects of a single intraperitoneal dose of 15 mg/kg of zinc chloride in aqueous solution on chromosome aberrations in bone marrow cells. While single fragment rearrangements were most commonly encountered in this system, no statistically significant differences in frequency were seen in treated animals compared to controls. The authors also tested the ability of zinc chloride to induce dominant lethal mutation in the germ cells of male mice. Three intact females were mated to zinc chloride injected mice for one week at time periods corresponding to the influence of the zinc chloride on mature sperm, late and early spermatids, late and early spermatocytes and spermatogonia. There were no zinc chloride-related effects on mortality before or after implantation. Also the percentage of effective matings, and numbers of corpora lutea, implantation sites, and live embryo were not affected.

Zinc chloride was studied for its ability to cause DNA strand breaks using the fluorescence analysis of DNA unwinding (FADU) technique with freshly isolated human white blood cells. McLean et al. (1982) reported that zinc chloride gave no firm evidence of DNA damage at a concentration of $5x10^{-5}$ M. In a similar study using the average molecular weight of DNA to determine strand breaks in Chinese Hamster Ovary (CHO) cells, Robison et al. (1982) also reported that zinc chloride caused no significant changes.

Rivedal and Sanner (1981) reported that zinc chloride was not an inducer of transformations in hamster embryo cells, and it had no effect on the frequency of transformation when tested in combination with benzo(a)pyrene.

When tested for induction of γ prophage in E. coli $WP2_s(\gamma)$, Rossman et al. (1984) reported that zinc chloride produced a two-fold increase (+/-) in γ prophage at a concentration of $3.2x10^{-3}$. In this system, positive inducers produced increases ranging from 3 to 75 times that of controls.

Zinc chloride did not produce preferential inhibition of DNA repair-deficient Bacillus subtilis M45 as compared to the DNA repair-competent parental strain, H17 (Nishioka, 1975).

b. Other Zinc Compounds

Zinc compounds were generally negative in in vitro reverse bacterial mutation assays with Salmonella typhimurium (Marzin and Vo Phi, 1985; Thompson et al., 1989); in mouse-mediated assays (Fabrizio, 1974); in the Escherichia coli assay (Nishioka, 1975); the mouse lymphoma forward mutation assay (Amacher and Paillet, 1980); and in in vivo rodent somatic and germinal cell cytogenetic assays (Fabrizio, 1974).

Zinc acetate (10-1,000 µg/mL) did not cause unscheduled DNA synthesis in cultured rat hepatocytes (Thompson et al., 1989).

Dose-related positive responses to concentrations of 1.3-13 µg/mL zinc acetate were seen in the $TK^{+/-}$ mouse lymphoma assay and in the in vitro Chinese Hamster Ovary (CHO) cell cytogenic assay both in the presence and absence of microsomal activation (Thompson et al., 1989).

Acceptable evidence of zinc sulfate-induced genotoxicity in yeast has been presented (Fabrizio, 1974). Oral administration of 2.75, 27.5, and 275.0 mg/kg zinc sulfate in both acute (one exposure) and subacute (five consecutive daily exposures) mouse host-mediated assays induced dose-related recombinogenic effects in Saccharomyces cerevisiae D3. For the acute study, recombinant frequencies (RF) ranged from $8.22x10^{-5}$ at the low dose to $13.22x10^{-5}$ at the high dose (RF for negative control, $4.06x10^{-5}$). For the subacute study, more pronounced effects were observed. The highest dose was both cytotoxic (30% reduction in total survivors) and recombinogenic (four-fold increase in the RF). The remaining doses were not cytotoxic, but the RF was increased 2-fold at the low dose and 2.8-fold at the intermediate dose.

7. Carcinogenicity

a. Zinc Chloride

Administration of zinc chloride in drinking water did not promote kidney or liver lesions when administered in drinking water for 25 weeks.

Kurokawa et al. (1985) treated a group of 7-week old male F344 rats (15/group) with zinc chloride (96% pure) at 450 ppm in drinking water (equivalent to ≈ 28 mg/kg/day based on body weight and intake data provided) for 25 weeks. Prior to zinc chloride exposure, another treatment group received 500 ppm of N-ethyl-N-hydroxy-ethylnitrosamine (EHEN) in drinking water for 2 weeks. Two additional groups either received drinking water (DW) alone or DW following initiation with EHEN. Mean final body weight for the EHEN-zinc chloride group were significantly lower ($p<0.01$) than the group receiving drinking water alone, but were not significantly different from the EHEN-DW controls. Mean final body weight for the DW-zinc chloride group were comparable to both control groups. There were no significant differences in absolute kidney or liver weights in either of the zinc chloride groups. The relative kidney weights of both the initiated and uninitiated zinc chloride groups were significantly increased as compared to the DW only controls ($p<0.05$). However, these differences were minor (0.61 versus 0.60). Mean intake of drinking water (mL/rat/day) were slightly lower in both groups receiving zinc chloride as compared to either control group.

The EHEN-DW controls exhibited the same significant increase in relative kidney weight when compared to the DW controls. Renal tissue was examined for preneoplastic and neoplastic lesions. The lesions were classified as dysplastic foci (DF) or renal cell tumor (RCT). Dysplastic foci were defined as proliferation of lining epithelium of solitary tubules ranging from a focal increase in cell numbers to complete obliteration of the tubules and included dilated tubules with multilayered epithelium or the projection of lining cells into the lumen (Kurokawa et al., 1985). While there was no significant difference in the incidence of DF between the EHEN-zinc chloride and EHEN-DW rats, the mean number of DF/cm^2 was significantly increased ($p<0.01$) in the EHEN-zinc chloride group as compared to the control group. There were no significant differences in either the incidence or the mean number of RCTs of the EHEN-zinc chloride or EHEN-DW groups. Renal cell tumors were single or multiple nodules usually with a solid growth pattern but occasionally presenting as cystic formations with papillary-like ingrowth or tumors with trabecular morphology. All RCTs were benign. Neoplastic nodules and hepatocellular carcinomas were observed in the livers of both the zinc chloride and DW rats initiated with EHEN but no significant differences were found between these two treatment groups. No lesions were observed in the rats receiving only DW or zinc chloride without prior initiation. Based on the results of this study, the authors concluded that zinc chloride could not be considered a promoter of kidney lesions.

Testicular tumors (embryonal carcinomas) were observed in 2 of 49 Syrian hamsters administered 2 mg zinc chloride by a single intratesticular injection at 8-14 weeks (during rapid gonadal growth) (Guthrie and Guthrie, 1974). All but six animals exhibited testicular pathology, such as fibrous-walled cavities near the epididymis and areas of coagulative necrosis in testes surrounded by a zone of pigmented and foamy macrophages. The two tumors arose adjacent to the area of necrosis (Guthrie and Guthrie, 1974).

VII. HEALTH ADVISORY DEVELOPMENT

Zinc is an essential trace element which is a constituent of a number of enzymes involved in key biological processes. Zinc deficiency is associated with loss of appetite, growth retardation, skin changes, immunological abnormalities, wound healing retardation, and developmental effects (NAS 1989). The development of a health advisory is complicated by the fact that there appears to be a narrow range of doses between the amount of zinc needed to fulfill physiological needs (5.5 mg/day) and the amount that will produce minimally adverse effects (depressed E-SOD at 60 mg/day) (King, 1989; Fischer et al., 1986; Yadrich et al., 1989). The Recommended Dietary Allowance for zinc ranges from 5 mg/day for infants to 19 mg/day for lactating women (NAS, 1989). These values were used as a guide for Health Advisory derivation.

Available data on the oral exposure of humans and animals to various forms of zinc compounds have been reviewed. In animals (rats, mice, and guinea pigs), oral LD_{50}'s and average lethal doses range between 200 and 1,000 mg/kg. Results of exposure to zinc chloride while being fed a synthetic diet deficient in pantothenic acid, as well as those following exposure via drinking water for 25 weeks are reported. Both reproductive and teratogenic effects have been evaluated. No bioassay for carcinogenicity has been located in the literature, but a study of the tumor-promoting potential of zinc chloride is discussed. Human exposure to zinc chloride, both by ingestion and inhalation, are reported. Tissue damage has been indicated upon both ocular and dermal exposure, and a low dermal absorption rate has been indicated.

Oral intake of an estimated zinc chloride dose of 1,000 mg/kg in humans resulted in gastrointestinal (GI) symptoms which included burns of the mouth and throat, abdominal pain and vomiting with blood in the vomitus and urine (Markwith, 1940; Chobanian, 1981; Potter, 1981). Vomiting and diarrhea occurred in people who ingested approximately 225 mg (3.2 mg/kg) or greater of zinc leached from galvanized containers. (Brown, 1964). Gastrointestinal distress is associated with doses of 50-150 mg/day (0.7-2.1 mg/kg/day of zinc acetate or sulfate) (Freeland-Graves et al., 1982; Prasad et al., 1978; Samman and Roberts, 1988). A number of human studies have reported that zinc (sulfate or gluconate) doses ranging from 29-311 mg/kg (0.4-4.4 mg/kg/day) for longer-term exposures decrease serum HDL, erythrocyte superoxide dismutase, copper, and ceruloplasmin levels (Black et al., 1988; Chandra 1984; Fischer et al., 1984; Goodwin et al., 1955; Hooper et al., 1980; Samman and Roberts, 1988). In addition anemia and neutropenia have been reported in some people following doses of 43-200 mg/day zinc (sulfate or acetate) (0.6-2.8 mg/kg/day) for longer-term exposures (Hoffman et al., 1988; Prasad et al., 1978; Simon et al., 1988).

Mucosal damage is the most consistent effect reported after exposure to high doses of zinc chloride by both the oral and inhalation route. Rats and rabbits receiving single oral doses of zinc chloride solution at doses between 250 and 1,000 mg/kg developed perforations of the stomach, penetration into the liver and pyebric stenosis (Hahn and Schunk, 1955). The only notable effect reported following short-term exposure of animals to zinc chloride were symptoms of pantothenic acid deficiency. This effect was evidenced mainly by severe alopecia and weight loss in rats maintained on a synthetic diet and orally administered approximately 100 mg/kg/day zinc chloride and a pantothenic acid-deficient vitamin supplement (Gross et al., 1941). A slight decrease in the intake of drinking water was reported in rats exposed to

28 mg/kg/day zinc chloride in that medium for 25 weeks (Kurokawa et al., 1985). Histological changes were reported in the kidneys of rats exposed to 190.6 mg/kg/day zinc chloride for 90 days (Llobet et al., 1988).

No effects on reproductive parameters were seen in rats exposed to 125 or 250 mg/kg/day zinc chloride as the acetate salt in the diet during breeding and through production of one generation (Heller and Burke, 1927). Offspring were also treated and bred without notable effects. Zinc chloride (150 mg/kg/day) was considered an equivocal teratogen based on a slight but significant reduction in live litter size, but only when the live litters found in utero were included in the determination of litter size (Seidenberg et al., 1986). Treatment of parental females on days 8-12 of gestation resulted in a significant decrease in average weight gain, as well as death of one of the maternal animals. Increases in resorption and fetal mortality have been reported in animals orally exposed to 150-1,000 mg/kg/day of zinc oxide, sulfate, or carbonate (Ketcheson et al., 1968; Kumar, 1976; Sutton and Nelson, 1937). Zinc deficiency also adversely affects reproductive function, and fetal development (Hurley, 1969; Hurley and Swenerton, 1966; Hurley et al. 1971; Rogers et al. 1985).

Dermal irritation studies resulted in the development of severe edema and necrotic erythema following application of a 10% solution of zinc chloride to the shaved skin of rabbits. Mild conjunctivitis with moderate corneal opacity developed after instillation of this solution into the eye (William, 1984). Johnstone et al. (1973) indicated that zinc chloride solution acted as a denaturant or fixative when applied to the cornea. Evidence of dermal absorption was indicated by a reduced weight gain in guinea pigs after percutaneous administration of an aqueous solution (Wahlberg, 1965). An absorption rate of <1% over a five hour period was indicated.

No evidence of tumor promotion was reported in male F344 rats given 28 mg/kg/day zinc chloride in drinking water for 25 weeks (Kurokawa et al., 1985). Equivocal evidence of testicular tumors was reported in hamsters intratesticularly injected with 2 mg zinc chloride (Guthrie and Guthrie, 1974). Mutagenicity studies were inconclusive although most test results were negative. Some evidence of cytotoxicity was seen during mutagenic assays (DeKnudt and Deminatti, 1978; McGregor, 1980).

A. Quantification of Toxicological Effects

Health Advisories are generally determined for one-day, ten-day, longer-term (approximately 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{\text{(NOAEL or LOAEL) (BW)}}{\text{(UF(s)) (\_\_\_ L/day)}} = \text{\_\_\_\_mg/L (\_\_\_\_ µg/L)}$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100 or 1,000), in accordance with NAS/EPA guidelines.

L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

The health advisory levels which follow were derived with both the essentiality and toxicity of zinc in mind. In doing so, the most recent set of Recommended Daily Allowances (RDAs) for zinc, derived by NRC (1989), were used as a guide in the overall risk assessment analysis. If traditional procedures for developing RfDs are applied to the available data (uncertainty factors of 100-1,000 applied to less-than-lifetime human study end points), the resulting RfDs for zinc would be considerably lower than the RDAs. With these parameters in mind, the following numbers were derived.

1. One-Day Health Advisory

The oral LD_{50} for zinc sulfate in rats was 920 mg/kg, and the oral LD_{50} for zinc chloride in rats, mice and guinea pigs ranged from 200 to 502 mg/kg (Fabrizio, 1974; Calvery, 1942; Yakuri, 1974). One-time ingestion of zinc in beverages at 4.6 mg/kg produced severe abdominal and gastric symptoms in adult humans (Brown et al., 1964). However, since this value was derived from a case study of zinc-induced food illness in adults, the accuracy of the dose information is questionable. Thus, the LD_{50} values and food poisoning doses are not appropriate for the calculation of the One-day Health Advisory for zinc. Therefore, the RDA for a 1-year-old, 9-kg infant (5 mg/day) is used as the basis of the One-Day HA value calculated below.

$$\text{One-day HA} = \frac{(0.56 \text{ mg/kg/day})\ (10 \text{ kg})}{(1)\ (1 \text{ L/day})} = 5.6 \text{ mg/L (rounded to 5 mg/L to correspond to infant RDA)}$$

where:

0.56 mg/kg/day = RDA for a 9-kg infant.

10 kg = assumed weight of child.

1 = uncertainty factor, chosen in accordance with NAS/EPA guidelines for use with an RDA which provides adequate zinc for human growth and nutrition (NAS, 1989).

1 L/day = assumed daily water consumption by a 10-kg child.

This value is expected to be without any adverse effect even when the diet contains zinc. The RDA for the slightly heavier 13-kg child is 10 mg/day.

2. Ten-Day Health Advisory

No suitable information was found in the available literature for determining the Ten-day HA for zinc for a 10-kg child. The One-day Health Advisory of

5 mg/L, based on the RDA for a 9-kg infant is suitable for use as the Ten-day HA.

3. Longer-Term Health Advisory

Studies by Fischer et al. (1984) and Yadrick et al. (1989) concerning the effects of zinc on copper homeostasis were used as the basis of the Longer-term Health Advisory. In these studies, healthy adults were given 25 mg of zinc as the gluconate twice daily for 6 or 10 weeks. There was a significant decrease in erythrocyte-superoxide dismutase (E-SOD) activity or concentration at both 6 and 10 weeks of exposure (Fischer et al., 1984; Yadrick et al., 1989). The decreased concentration of E-SOD is indicative of a copper deficiency and a diminished capacity of the cells to respond to oxidative stress. There were no differences in serum copper levels or ceruloplasmin activity as compared to the controls. Serum zinc levels were significantly increased; dietary zinc was not measured. The total zinc intake of 66 mg/day (dietary intake of 16 mg zinc/day plus a zinc supplement of 50 mg/day) resulted in a LOAEL of 0.94 mg/kg/day for a 70 kg male (Fischer et al., 1984). For females, the total zinc intake was 59.7 mg/day or a LOAEL of 1.0 mg/kg/day for a 60-kg female with a dietary intake of 9.7 mg/day (Yadrick et al., 1989).

Similar findings were seen in females, but not males, administered 150 mg zinc/day for 6 weeks during a double blind placebo study (Samman and Roberts, (1988). Ceruloplasmin, E-SOD and Cu-Zn-SOD concentrations were all significantly decreased during the zinc supplement period when compared to the values during placebo administration. There was a 20% decrease in E-SOD and a 23% decrease in Cu-Zn-SOD at the end of 6 weeks. The same parameters were very slightly (but not significantly) decreased in the males.

The results from several case studies, in which zinc supplementation for periods of 10 months to 2 years resulted in symptoms of a copper deficiency, support the data by Fischer et al. (1984); Samman and Roberts, (1988); and Yadrick et al. (1989). Male and female patients experienced anemia and neutropenia with ingestion of 43-200 mg zinc per day for 10 months to 2 years. (Hoffman et al., 1988; Prasad et al., 1978; Simon et al., 1988). Serum zinc levels were high and ceruloplasmin values were low. Both the anemia and neutropenia were resolved after zinc supplementation ceased.

The LOAEL from the study by Yadrick et al. (1989) in adult females was used to calculate the Longer-term HA for a 10-kg child as follows:

$$\text{Longer-term HA} = \frac{(1.0 \text{ mg/kg/day})\ (10 \text{ kg})}{(3)\ (1 \text{ L/day})} = 3.33 \text{ mg/L (rounded to 3 mg/L)}$$

where:

1.0 mg/kg/day = LOAEL, based on a depression of E-SOD concentrations in human subjects following exposure to zinc for 10 weeks (Yadrick et al., 1989).

10 kg = assumed weight of child.

3 - uncertainty factor, chosen in accordance with NAS/EPA guidelines for use with a LOAEL from a human study. This factor also takes into account that zinc is essential for human growth and nutrition. [The RDA for a child ranges from 5 to 10 mg zinc/day (NRC, 1989).]

1 L/day - assumed daily water consumption by a 10-kg child.

Using the Yadrick et al. (1989) LOAEL, the Longer-term HA for a 70-kg adult is calculated as follows:

$$\text{Longer-term HA} = \frac{(1.0 \text{ mg/kg/day})\ (70 \text{ kg})}{(3)\ (2 \text{ L/day})} = 11.6 \text{ mg/L}$$

(rounded to 12 mg/L or 12,000 µg/L)

where:

1.0 mg/kg/day - LOAEL, based on a depression of E-SOD concentrations in human subjects following exposure to zinc for 10 weeks (Yadrick et al., 1989).

70 kg - assumed weight of adult.

3 - uncertainty factor, chosen in accordance with NAS/EPA guidelines for use with a LOAEL from a human study This factor also takes into account that zinc is essential for human growth and nutrition. [The RDA for an adult ranges from 12 to 19 mg zinc/day (NRC, 1989).]

2 L/day - assumed daily water consumption by a 70-kg adult.

4. Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three-step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC

from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed.

If the contaminant is classified as a known, probable or possible carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution must be exercised in making a decision on how to deal with possible lifetime exposure to this substance. For human (A) or probable human (B) carcinogens, a Lifetime HA is not recommended. For possible human carcinogens (C), an additional 10-fold safety factor is used to calculate the Lifetime HA. The risk manager must balance this assessment of carcinogenic potential and the quality of the data against the likelihood of occurrence and significance of health effects related to noncarcinogenic end points of toxicity. To assist the risk manager in this process, drinking water concentrations associated with estimated excess lifetime cancer risks over the range of 1 in 10,000 to 1 in 1,000,000 for the 70-kg adult drinking 2 L of water/day are provided in the Evaluation of Carcinogenic Potential section.

In establishing an RfD for zinc, the data on essential needs were combined with the human data on toxic responses in studies of limited duration in order to define a transition level which would meet the physiological requirements of nearly all healthy persons without causing a toxic response in the most sensitive population subgroup when consumed daily for a lifetime.

There appears to be only an order of magnitude between the amount of zinc that will satisfy physiological need (5.5 mg/day; King, 1989) and the amount that is associated with the appearance of minimally adverse effects (depress E-SOD at 60 mg/day) with 6- to 10-week daily exposures (Fischer et al., 1986; Yadrich et al., 1989). Since an appropriate lifetime duration study was not available and the animal data from the 12-month duration study by Aughey et al. (1977) did not evaluate the sensitive end points of zinc toxicity identified in the human studies, the LOAEL of 1.0 mg/kg/day which was used for the Longer-term HA is also used for determination of the RfD and DWEL as follows:

Step 1. Determination of the Reference Dose (RfD)

$$RfD = \frac{(1.0 \text{ mg/kg/day})}{(3)} = 0.33 \text{ mg/kg/day (rounded to 0.3 mg/kg/day)}$$

where:

1.0 mg/kg/day = LOAEL, based on a depression of E-SOD concentrations in human subjects following 10-week exposure (Yadrick et al., 1989)

3 = uncertainty factor, chosen in accordance with NAS/EPA guidelines for use of a LOAEL from a human exposure study (of an essential nutrient) in which minimally adverse effects were observed.

This RfD was compared to the RDA expressed on a mg/kg/day basis for each age and sex group. For 79% of a 70-year lifetime, the RDA corresponds to a daily zinc intake of 0.23 mg/kg/day or less, a value which provides the functional and metabolic zinc requirements for over 99% of the population (NAS, 1989).

The RfD of 0.3 mg/kg/day supplies adequate zinc to meet these requirements over a lifetime without any concurrent physiologic impairment. It does not supply the RDA for infants, preadolescent children and pregnant women and, therefore, does not apply to these groups. The RfD dose is expected to be without adverse effect when consumed on a daily basis over an extended period of time. It neither induces a nutritional deficiency in healthy nonpregnant adult humans consuming the average American diet nor causes undesirable inhibition of copper absorption.

Step 2. Determination of the Drinking Water Equivalent Level (DWEL)

$$DWEL = \frac{(0.3 \text{ mg/kg/day})\ (70 \text{ kg})}{(2)\ (1 \text{ L/day})} = 10.5 \text{ mg/L (rounded to 10 mg/L)}$$

where:

0.3 mg/kg/day = RfD.

70 kg = assumed weight of adult.

2 L/day = assumed water consumption by 70-kg adult.

Step 3. Determination of the Lifetime HA

$$\text{Lifetime HA} = (10 \text{ mg/L})\ (0.2) = 2.0 \text{ mg/L}$$

where:

10.0 mg/L = DWEL.

0.2 = assumed percentage of the daily exposure (20%) contributed by the ingestion of drinking water.

According to NAS (1989), approximately 70% of the zinc consumed in human diets comes from animal products. Drinking water in the U.S. generally contains less than 0.1 mg zinc/liter.

B. Quantification of Carcinogenic Potential

Due to the absence of toxicological evidence for classifying zinc as a potential carcinogen, a quantification of carcinogenic risks for zinc is inappropriate.

Groups of male F344 rats (15/group) were given 450 ppm (approximately 28 mg/kg/day) of zinc chloride in drinking water for 25 weeks to evaluate the promoting effect on renal tumorigenesis (Kurokova et al., 1985). Some animals were pretreated with N-ethyl-N-hydroxyethylnitrosamine (EHEN) (500 ppm) as an initiator. Four groups were compared: controls (no EHEN or zinc chloride), EHEN-DW, EHEN-zinc chloride and DW-zinc chloride. There were no significant differences in the incidence of dysplastic foci (DF) between the EHEN-zinc chloride and EHEN-DW groups. The mean number of DF/CM^2 was increased significantly ($p<0.01$) in the EHEN-zinc chloride group compared to controls. There were no significant differences between groups for the occurrence of renal cell tumors and hepatocellular carcinoma. Even though this study is

limited by duration and use of one sex, it did not demonstrate that zinc chloride is a promoter of kidney lesions.

Other limited available information on the carcinogenic potential of zinc (testicular tumors in 2/49 hamsters from intratesticular injection) is particularly relevant to zinc exposure via drinking water.

Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), zinc and zinc salts are assigned to Group D: not classifiable as to human carcinogenicity. This category is for agents with inadequate animal evidence of carcinogenicity.

VIII. OTHER CRITERIA, GUIDANCE AND STANDARDS

A. Zinc Chloride

The ACGIH (1986) 8-hour time weighted average threshold limit value (TWA-TLV) for exposure to zinc chloride is 1 mg/m^3. This limit is protective against the irritative effects that result from exposure to zinc chloride fume. A short-term exposure limit (STEL) of 2 mg/m^3 also has been recommended. The Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL) for zinc chloride fume also has been set at 1 mg/m^3 averaged over an 8-hour work shift (Mackison et al., 1981). An initial or pre-employment medical examination is recommended to detect pre-existing conditions with examination of the respiratory system stressed. In 1978, the exposure limit in Sweden was also 1 mg/m^3 (ACGIH, 1986).

Cullumbine (1957) calculated "safety distances" for exposure to zinc chloride screening smoke for set time periods under the differing meteorological conditions of day and night exposure. For daytime exposure, a distance of 91 meters from the source for 43 minutes is considered safe while at 914 meters exposure could last up to 37 hours. Estimated zinc chloride concentrations at these distances are 47 and 0.9 mg/m^3, respectively. Under night time conditions, a distance of 183 meters from the source would be considered safe for up to 24 minutes and 914 meters would be a safe distance for exposures up to 2.5 hours. Zinc chloride levels at these two distances are estimated at 85 and 13 mg/m^3, respectively (cited in Hill et al., 1978).

B. Other Zinc Compounds

The current EPA-recommended secondary standard based on taste and odor for zinc in drinking water is 5 mg/L (NRC, 1979).

Although standards for public exposure are not reported (NRC, 1979), air quality standards for zinc and its compounds have been established for occupational exposures in many countries, including the United States. For example, the American Conference of Governmental Industrial Hygienists recommends a Threshold Limit Value-Time Weighted Average (TWA) of 1 mg/m^3 for zinc chloride fumes and a Threshold Limit Value-Short-Term Exposure Limit (STEL) of 2 mg/m^3 (ACGIH, 1990). The corresponding values for zinc oxide fumes are 5 mg/m^3 and 10 mg/m^3 and there is a TWA of 10 mg/m^3 for zinc oxide.

The Recommended Daily Allowance for zinc is 5 mg for infants under 1 year of age; 10 mg for children under 10 years; 15 mg for adult males; 12 mg for adult females; 15 mg for pregnant women; and 16-19 mg for lactating women (NRC, 1989).

No other criteria, guidelines or standards pertaining to zinc exposure via drinking water were found.

IX. ANALYTICAL METHODS

The concentrations of zinc in environmental media can be determined by several methods based on either emission or absorption spectroscopy. Each of these methods can be used for the determination of a number of metals and is not specific for zinc or zinc chloride. In each of the methods the metal is dissolved using acid digestion and is then thermally excited. All elements, when excited, emit or absorb light frequencies characteristic of that element and those frequencies can be used to identify the element. Most metal analysis is done in the ultraviolet and x-ray regions of the spectrum.

EPA Method Number 289.1 uses atomic absorption (AA) spectroscopy to determine the zinc concentration in water and wastewater. In this method the dissolved metals are aspirated into a flame source and excited to the point that the metals are dispersed to a mono-atomic state. A light source, whose cathode is the metal of interest, passes through the flame; the resulting absorption of light by the element of interest is directly proportional to concentration. The disadvantage of this technique, when multiple metal ions are present in the solution, is the fact that only one metal can be detected during an analysis. The detection limit of this technique is 5.0 µg/L for zinc (EPA, 1979).

EPA Method Number 289.2, Graphite Furnace Atomic Absorption (GFAA), is an alternate atomic absorption technique for use with water and wastewater. In this approach, a specific amount of liquid is dried on a thermal source to concentrate the sample. The sample is then electrothermally excited for analysis and identification. The detection limit for zinc is 0.05 µg/L (EPA, 1979).

Inductively-Coupled Plasma Atomic Emission Spectroscopy (EPA Method Number 200.7) is a method which is applicable for the analysis of dissolved and/or suspended metals in water or wastewater. In this technique the liquid sample is aspirated into the flame source which is a plasma torch of argon excited to super hot levels by radio-frequency (RF) radiation. The metals are excited to the level where they emit radiation. By using classical dispersion grating optics, the intensities of the spectral lines are monitored by a photomultiplier tube. The spectral lines and their intensities are used to identify the metal and its concentration in the sample. One advantage of this techniques is that a large number of metals can be determined simultaneously; however, in samples with multiple analytes, interferences between analytes can sometimes limit the accuracy of the results. The detection limit for zinc in this method is 2.0 µg/L (EPA, 1982).

In EPA Method Number 6020, Inductively-Coupled Plasma Mass Spectroscopy (ICP/MS), the excitation of the metal is again by a radio-frequency plasma, but the excited atoms are then interfaced into a mass spectrometer (MS) where they are sorted according to their mass/charge ratios for identification and quantification. The use of the mass spectrometer makes the method applicable for determination of a large number of elements in water and wastewater at low concentrations. The detection limit for zinc is 0.08 µg/L. Quantification is achieved by computerized software programs similar to those used in EPA-MS methods for analysis of organic compounds. By using appropriate filtration and digestion steps, this method can be used to measure both dissolved and particulate metals in water samples (EPA, 1990).

Neutron activation is used to determine the concentration of zinc in biological samples (Greenberg et al., 1979; Jurgensen and Behne, 1977; Lievens et al., 1977). The samples are irradiated by exposure to a high neutron flux to form radioactive ^{69}Zn and then wet-ashed with concentrated sulfuric acid and extracted with a diphenylthiocarbazone solution. The zinc concentration is determined by a measurement of gamma ray emissions with a scintillation counter used in conjunction with a pulse height analyzer and then quantified by comparison with a standard containing a known amount of ^{69}Zn (Lieberman and Kramer, 1970). The detection limit of this method for zinc varies with the medium analyzed. A detection level of 5E-5 µg/100 mL has been reported for blood samples (Jurgensen and Behne, 1977).

X. TREATMENT TECHNOLOGIES

Zinc chloride in water is rapidly hydrolyzed to zinc ions (Zn^{++}) and chloride ions (Cl^{-}); no specific treatment of water for removal of zinc chloride is necessary. The ionic zinc reacts to form various hydroxides and zincates. Removal of zinc from water can be accomplished by standard water treatment techniques, such as coagulation and filtration.

Available data indicate that reverse osmosis (RO), chemical coagulation and possibly ion exchange (IX) will significantly reduce zinc levels in drinking water.

Foster et al. (1980) applied RO treatment to saline water with a zinc concentration of 0.26 mg/L in Alamogordo, New Mexico. The RO system consisted of hollow fiber (HF) and spiral wound (SW) elements. The HF was operated at 515 psi with a water recovery rate of 78%, while the SW was operated at 430 psi with a water recovery rate of 79%. The HF element removed 73% of zinc while the SW removed 92%.

Fox and Sorg (1987) tested the effectiveness of home-use reverse osmosis devices in removing zinc. RO systems typically consist of prefilters, dechlorinators, a RO module and an activated carbon filter. The RO module, a spiral-wound polyamide filter, was operated at a pressure of 42 ± 2 psig. Zinc was reduced by 99% from an influent concentration of 5.42 mg/L.

Harries (1985) described the performance of a seeded RO pilot plant used to desalinate gold mine water nearly saturated with $CaSO_4$. The pilot plant was operated for 5,000 hours at a water recovery rate of 92-96%. Tubular cellulose acetate membranes were operated at 400 psi. Zinc was reduced by 81.8% from an influent concentration of 2.2 mg/L.

Terril and Neufeld (1983) reported data from a RO unit used to treat blast furnace scrubber effluent which, in this case, had a zinc concentration of 27 mg/L. The RO unit contained cellulose acetate (CA) membranes and was operated at pressures of 350-450 psi and a water recovery rate of 70-80%. The system achieved 99% reduction in zinc levels.

Hrubec et al., (1979) reported the results of wastewater treatment by RO for water reuse. The RO system contained CA membranes in tubular configuration and was operated at 580 psi and a water recovery rate of 60-80%. Zinc was reduced by 75% from an influent concentration of 40 mg/L.

Hrubec et al., (1979) reported that wastewater treatment by lime softening reduced zinc by 92% from an influent concentration of 119 mg/L. Lime [at 250-600 mg $Ca(OH)_2$/L] and polyelectrolyte (at 0.5 mg/L) were added to the rapid mix and flocculator influent at a pH of 11.2. Retention time for the clarifier was 1.5 hours. Recarbonation was carried out in columns designed for an optimum hydraulic time. Filtration was accomplished on a double-layer filter bed.

Adams et al. (1975), demonstrated that when dissolved zinc was added to the influent of a wastewater treatment plant at levels of 2.5 to 20 mg/L, primary treatment removed only about 8 to 14% of the zinc. After activated sludge treatment, however, 74 to 96% of the zinc was removed. It is uncertain whether the zinc was bioaccumulated by the microorganisms, or if further

removal of solids by sludge formation was responsible for the dramatic reduction in zinc concentration. Nevertheless, it is clear that in the biodensity ranges found in sewage treatment plants, zinc is effectively removed from solution, and bioaccumulation probably plays an important role in such removal.

Laboratory jar tests were conducted to develop data on the removal of metal ions, including zinc, from aqueous solutions (Westbrook and Grohse, 1979). Sodium sulfide was added at stoichiometric ratios of 1.1 and 1.5. From an initial concentration of 5 mg/L, zinc was reduced to below 1 mg/L by precipitation with sodium sulfide.

The performance of natural zeolite clinoptilolite, used as an ion exchange resin, was studied in a pilot plant by Blanchard et al. (1984). Two columns, each approximately 8 inches in diameter and packed with 40 inches of zeolite, were operated in series. The breakthrough concentration was set at 50 µg/L for zinc, after which the zeolite was regenerated with NaCl solution at a flow rate of 10 bed volumes (BV) per hour. Zinc breakthrough occurred after 220 BV with a leakage rate of 8 µg/L at an influent concentration of 0.235 mg/L.

XI. CONCLUSIONS

Based on the available animal toxicity data, the HA for One-day and Ten-days is 5 mg/L for the 10 kg child. The Longer-term HA for the 10 kg child is 3 mg/L and for the 70 kg adult is 10 mg/L. The Lifetime HA is 2 mg/L. These values are considered protective against toxic effects for the most sensitive members of the population. The essentiality of zinc was considered in the derivation of these HA values. Currently, adequate available data to assess the carcinogenic risk of zinc are inadequate but in view of its physical and chemical properties, and considering that zinc is an essential element, it seems unlikely that zinc chloride will present a carcinogenic risk to humans at the levels considered safe for consumption. Using the EPA criteria for classification of carcinogenic risk, zinc chloride and other zinc compounds currently meet the criteria for category D, not classifiable as to human carcinogenicity. This category is for agents with inadequate human and animal evidence of carcinogenicity or for which no data are available.

A companion report, "Data Deficiencies/Problem Areas and Recommendations for Additional Data Base Development for Zinc Chloride" (Appendix 1), summarizes the scope of existing data reviewed for this HA. Recommendations are made for additional studies to assess the short term effects of zinc chloride in drinking water as well as developmental toxicity studies to clarify the issue of the teratogenicity of zinc chloride.

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APPENDIX 1

Data Deficiencies/Problem Areas and Recommendations for Additional Data Base Development for Zinc Chloride and other Zinc Compounds

INTRODUCTION

The Office of Water (OW), Environmental Protection Agency (EPA), in conjunction with the Department of the Army, has reviewed the available data on zinc and zinc chloride for the purpose of developing a Health Advisory (HA) useful in dealing with contamination of drinking water, to include "state-of-the-art" information on environmental fate, health effects and analytical methodology.

OBJECTIVES

The objective of this appendix is to provide an evaluation of the data deficiencies and/or problem areas encountered in the review process for zinc and to make recommendations, as appropriate, for additional data base development. This document is presented as an independent analysis of the current status of zinc technology, as related to its possible presence in drinking water, and includes a summary of the background information used in the development of the HA. For greater detail on the toxicology of zinc, the Health Advisory on Zinc Chloride should be consulted.

BACKGROUND

Zinc is an essential trace element which is a constituent of a number of enzymes involved in key biological processes. Zinc deficiency is associated with loss of appetite, growth retardation, skin changes, immunological abnormalities, wound healing retardation, and developmental effects (NAS, 1989). The development of a health advisory is complicated by the fact that there appears to be a narrow range of doses between the amount of zinc needed to fulfill physiological needs (5.5 mg/day) and the amount that will produce minimally adverse effects (depression of erythrocyte superoxide dismutase, E-SOD, at 60 mg/day) (King, 1989; Fischer et al., 1986; Yadrich et al., 1989). The Recommended Dietary Allowance for zinc ranges from 5 mg/day for infants to 19 mg/day for lactating women (NAS, 1989). These values were used as a guide for Health Advisory derivation.

In water, zinc compounds readily dissociate to its ionic form, combining with substances in the water to form hydroxides and insoluble precipitates. It has been detected only as trace amounts in most ground and surface waters (Hill et al., 1978). Hydrolysis is its main transformation process in the environment.

Few data are available on the pharmacokinetic properties of zinc in animals. Measurement of zinc chloride absorption in humans following µmol doses of zinc indicates that approximately 50-55% of the dose was absorbed (Payton et al., 1982). Minimal absorption was indicated following percutaneous application in guinea pigs (Skog and Wahlberg, 1964). Absorption following inhalation by five soldiers was indicated by an increase in plasma zinc levels (Hjortso et al., 1988). Distribution of zinc chloride to the tissues has been reported in both human (Hjortso et al., 1988) and animal studies (Feaster et al., 1955; Lorber et al., 1970; cited in Hill et al., 1978; Kossakowski and Grosicki, 1983) with levels highest in liver, kidney and intestines. Distribution to striated muscle also has been indicated (Sheline et al., 1943b). No data on the excretion of zinc following oral administration of zinc chloride was located in the literature but intravenous studies in mice, rats and dogs

indicated that most excretion takes place in the feces (Sheline et al., 1943a).

Data on the exposure of humans to zinc chloride, both orally and by inhalation, indicate that it is highly irritating to the mucous membranes (Potter, 1981; Chobanian, 1981). Death has been reported following inhalation of zinc chloride in a closed environment (Markwith, 1940; Evans, 1945; Milliken et al., 1963; Macaulay and Mant, 1963; Hjortso, 1988), usually as a result of toxicity to the respiratory tract. Toxic signs include inflammation with edema, bronchopneumonia with engorgement and necrosis (Evans, 1945). Sloughing of the epithelium also has been reported (Milliken et al., 1963; Macaulay and Mant, 1963). Exposure by inhalation in open spaces results in milder respiratory symptoms such as cough, hoarseness and sore throat, and also may include nausea, vomiting, fatigue and headache (Schenker et al., 1981). Reduced visual acuity and loss of the sense of smell has resulted from splash injuries from zinc galvanizing solutions (Houle and Grant, 1973).

In humans oral doses of zinc, approximately 225 mg (3.2 mg/kg) or greater leached from galvanized containers produce vomiting and diarrhea (Brown, 1964). Gastrointestinal distress is associated with doses of 50-150 mg/day (0.7-2.1 mg/kg/day as zinc acetate or sulfate) (Freeland-Graves et al., 1982; Prasad et al., 1978; Samman and Roberts, 1988). A number of human studies have reported that zinc sulfate or gluconate doses ranging from 29-311 mg/kg (0.4-4.4 mg/kg/day) for longer-term exposures decrease serum HDL, erythrocyte superoxide dismutase, copper, and ceruloplasmin levels (Black et al., 1988; Chandra 1984; Fischer et al., 1984; Goodwin et al., 1955; Hooper et al., 1980; Samman and Roberts, 1988). In addition anemia and neutropenia have been reported in some people following doses of 43-200 mg/day (0.6-2.8 mg/kg/day as zinc gluconate, -sulfate, or -acetate) for longer-term exposures (Hoffman et al., 1988; Prasad et al., 1978; Simon et al., 1988).

An oral LD_{50} and average lethal doses for zinc chloride were reported in animals. Yakuri (1974) reported an LD_{50} of 502 mg/kg in male mice while Woodard and Calvery (1941) as cited in Calvery (1942) reported acute oral median lethal doses of 350, 350 and 200 mg/kg in rats, mice and guinea pigs, respectively. Oral average lethal doses of 750 and 1,000 mg/kg were reported in rats and rabbits, respectively (Hahn and Schunk, 1955).

Dermal application of a 10% solution of zinc chloride to the skin of albino rabbits produced severe edema and necrotic erythema while mild conjunctivitis and moderate penetrating corneal opacity was evident after application to the conjunctival sac (Williams, 1984). Percutaneous administration of an aqueous solution of zinc chloride to guinea pigs resulted in a cessation of weight gain (Wahlberg, 1965). Johnstone et al. (1973) indicated that zinc chloride acted as a fixative and denaturant on excised bovine corneas.

Perforation of the stomach, penetration to the liver and pyloric stenosis occurred in rats and rabbits following a single oral dose in the 250-1,000 mg/kg zinc chloride range (Hahn and Schunk, 1955). Signs of vitamin deficiency evidenced by severe alopecia, growth retardation and rusting of the coat were precipitated after five weeks by the oral administration of zinc chloriac to female rats at a dose equivalent to approximately 100 mg/kg/day for a 40 kg rat (Gross et al., 1941). During this study, rats were maintained on a synthetic diet and orally administered a vitamin-supplemented filtrate fraction low in pantothenic acid.

No effects were seen in rats on reproductive parameters, offspring and the subsequent reproductive cycle of the offspring while exposed to 2.5-5% of zinc in the diet. A NOAEL of approximately 250 mg/kg/day was indicated (Heller and Burke, 1927). Seidenberg et al. (1986) reported that zinc chloride could be considered a teratogen based on a slight but significant reduction in live litter size, but only when live litters found in utero were included in the calculations. The oral dose in this study was 150 mg/kg/day in the drinking water and was administered on Days 8-12 of gestation. Average weight gain of the maternal rats was also significantly decreased at this dose level when compared to the controls. However, the study method was designed to screen chemicals for additional, more detailed, conventional evaluation; therefore, zinc chloride should be considered a potential teratogen.

In a study conducted to measure the tumor-promoting potential of zinc chloride, Kurokawa et al. (1985) treated young male rats at 450 ppm (approximately 28 mg/kg/day) in drinking water for 25 weeks, both with and without a prior two week initiation period with N-ethyl-N-hydroxyethylnitrosamine (EHEN). While the mean number of dysplastic foci were significantly increased at this dose level in the EHEN-initiated rats receiving zinc, there were no significant differences in the incidence of these lesions nor in the incidence or mean number of renal cell tumors. No effects were seen on final body weight and liver and kidney weight, nor were any lesions seen in the zinc-treated rats not initiated with EHEN.

Genotoxicity studies were somewhat inconclusive with most studies indicating no mutagenic effects with zinc chloride. Kalinina and Polukhina (1977) reported the occurrence of frame shift mutations. DeKnudt and Deminatti (1978) reported cytotoxicity in human lymphocytes and McGregor (1980) reported toxicity at high levels in S. typhimurium strains and in S. cerivisea. Dominant lethal mutation studies were negative (Vilkina et al., 1979).

Analysis for zinc can be accomplished by atomic absorption spectrophotometry (AAS), flameless AAS and neutron activation analysis. Calorimetric methods are also available. A detection limit of 10 µg/L in body fluids has been reported using AAS (Hill et al., 1978).

Based on the available animal toxicity data, the HA for One-day and Ten-days is 5 mg/L for the 10 kg child. The Longer-term HA for the 10 kg child is 3 mg/L and for the 70 kg adult is 10 mg/L. The Drinking Water Equivalent Level (DWEL) is 10 mg/L. The Lifetime HA is 2 mg/L. These values are considered protective against toxic effects for the most sensitive members of the population. The essentiality of zinc was considered in the derivation of these HA values. Currently, adequate available data to assess the carcinogenic risk of zinc are inadequate but in view of its physical and chemical properties, and considering that zinc is an essential element, it seems unlikely that zinc chloride will present a carcinogenic risk to humans at the levels considered safe for consumption. Using the EPA criteria for classification of carcinogenic risk, zinc chloride and other zinc compounds currently meets the criteria for category D, not classifiable as to human carcinogenicity. This category is for agents with inadequate human and animal evidence of carcinogenicity or for which no data are available.

DISCUSSION

Available data on the toxicokinetics, health effects, analysis and treatment of zinc have been reviewed.

While the toxicokinetic properties of zinc have not been extensively studied, available data indicate that humans absorb between 50-55% of an oral dose in the μmol range. Measurable zinc is distributed to the tissues with the largest amounts in the liver, kidney and intestines and lesser amounts in other tissues, including striated muscle. Excretion is primarily via the feces. Since zinc is an essential trace nutrient, its presence in the body is expected. Removal of excess quantities of zinc has been accomplished with the use of chelating agents. Further studies are not required for development of a HA.

Available studies on the toxicity of zinc include LD_{50} and average lethal doses. However, little data is available on the short-term exposure of animals to zinc by the oral route. Inadvertent ingestion of zinc soldering solutions has resulted in toxicity in humans. It is, therefore, recommended that studies be carried out in animals over periods ranging from several days to several weeks to determine a short-term NOAEL or LOAEL for zinc.

Oral exposure to zinc (various compounds) for longer periods of time indicate that doses of 29-311 mg/day (0.4-4.4 mg/kg/day) can produce marginally adverse effects on several blood chemistry parameters including decreased levels of HDL, erythrocyte superoxide dismutase, copper, and ceruloplasmin. Anemia and neutropenia may develop in more severe cases. Weight loss and vitamin deficiency have been demonstrated under conditions not routinely encountered, i.e. special synthetic diets. Available data is considered sufficient for development of a Longer-term and Lifetime HA.

While no bioassay for carcinogenicity of zinc has been conducted, preliminary studies to evaluate the tumor-promoting properties indicate that zinc chloride is not a promoter of tumors in the two organs in which zinc is readily distributed. Most genotoxic studies indicate that zinc is negative for mutagenicity.

Zinc chloride had no effect on the reproductive parameters nor on the offspring in a reproduction study. Mating of the litters of this study were also negative for reproductive effects. No further reproductive studies are recommended for HA development. Because zinc is a potential teratogen, based on a reduction of litter size when in utero live litters were counted, further studies on possible developmental effects should be undertaken.

Zinc is an essential trace element, and as a constituent of a number of enzymes, a participator in numerous biological processes. The National Academy of Sciences (NAS, 1989) has developed Recommended Dietary Allowances (RDAs) of 5-19 mg/day (0.3-0.6 mg/kg/day) for various populations.

Several methods for analysis of zinc in various matrices appear adequate for use in the detection of zinc in drinking water. No further studies are recommended. Similarly, development of techniques for the removal of zinc from water are not considered necessary at this time.

RECOMMENDATIONS

Based on the above discussion, the following recommendations are made:

1. The available studies on the short-term toxicity of zinc are limited. It is recommended that short-term exposure studies in one or more animals species be conducted to confirm safe exposure levels to zinc in water for development of One-day and Ten-day HAS.

2. Available data on the developmental effects of zinc in animals indicate that it is an equivocal teratogen. It is recommended that further studies be conducted to clarify its developmental effects.

3. A lifetime bioassay in male and female rodents, at least five species, should be conducted to determine the carcinogenic potential of zinc.

4. Aside from the aforementioned data gaps, no further studies on zinc, as related to its possible presence in drinking water, are deemed necessary at this time.

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